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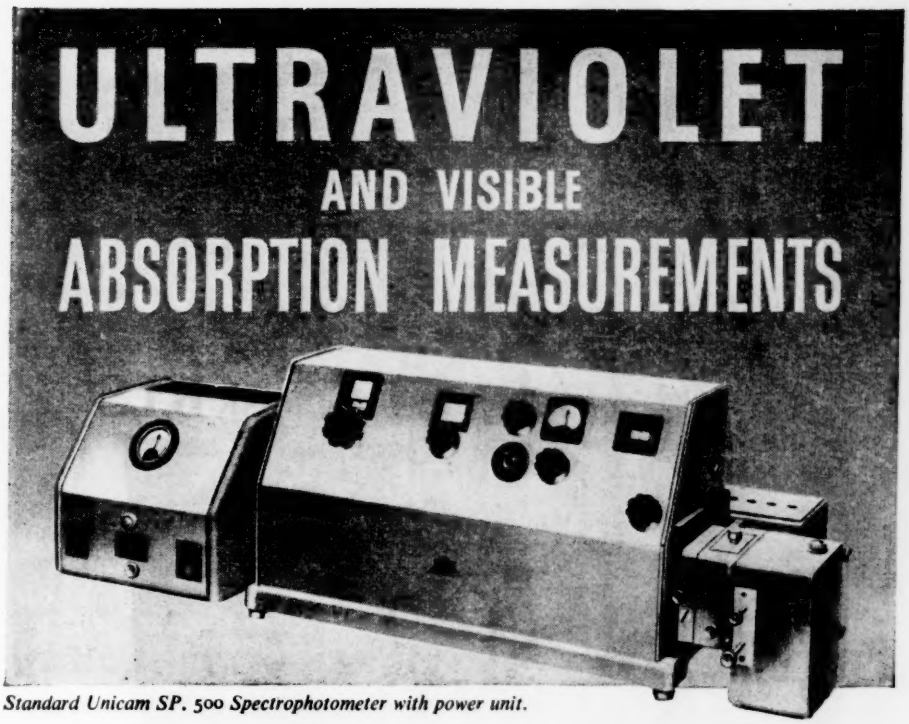

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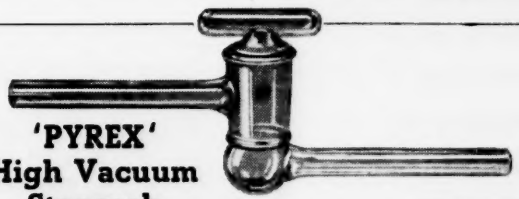

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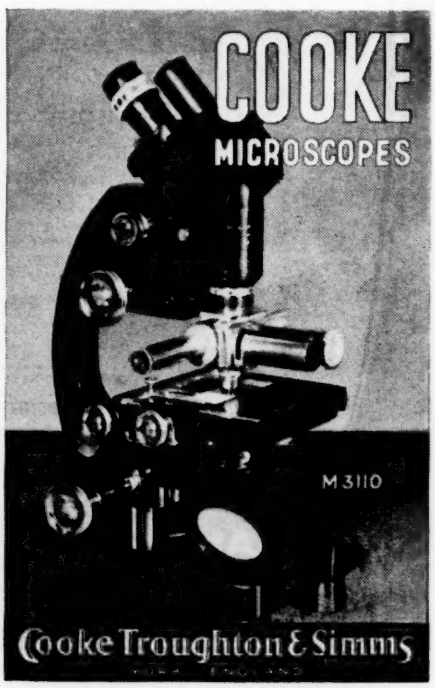

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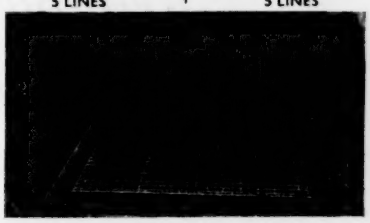

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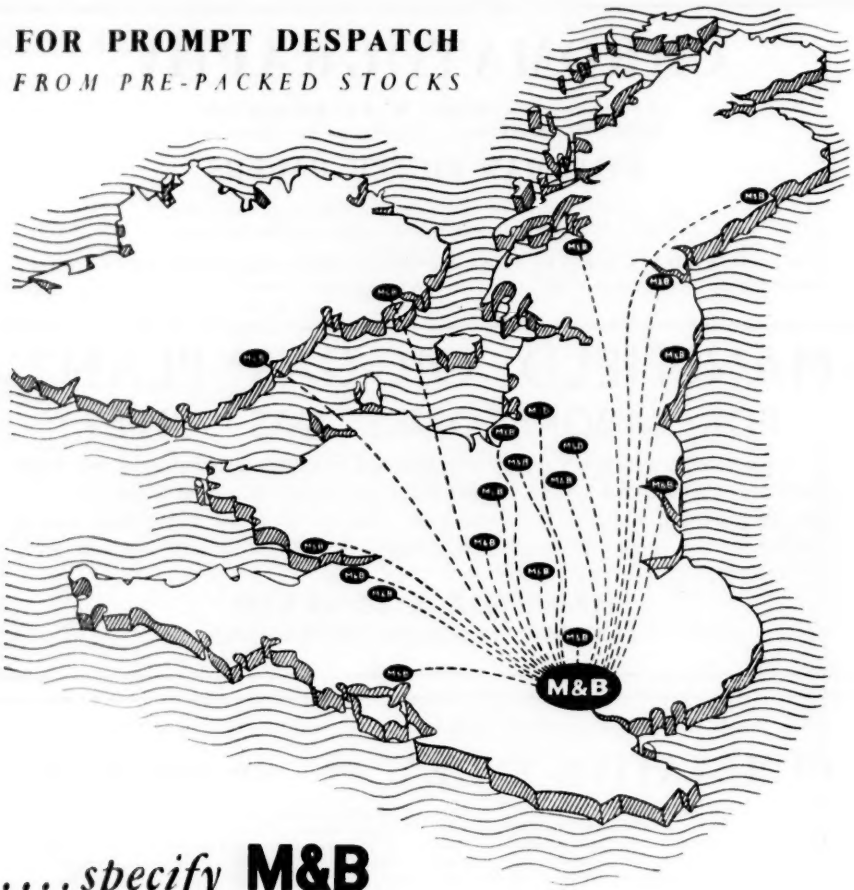

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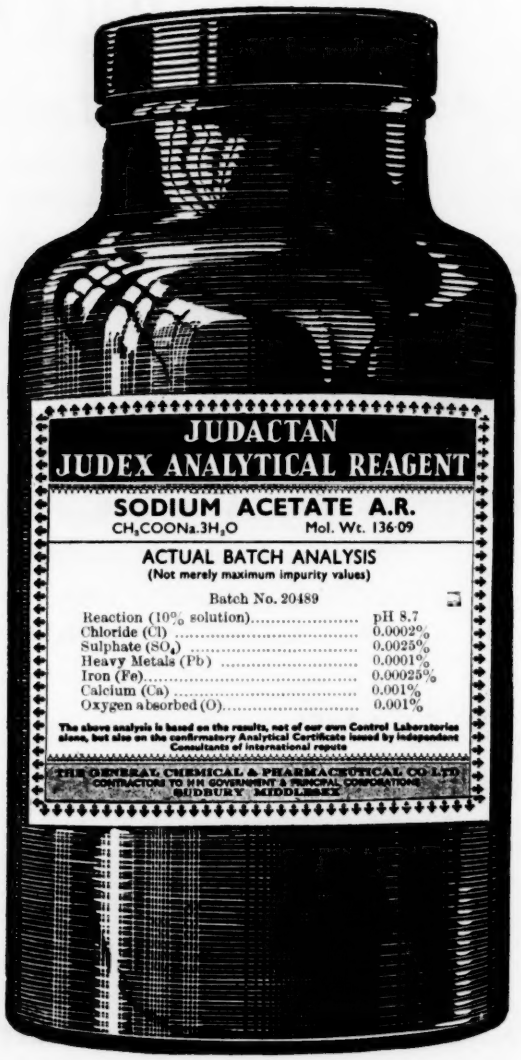
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ERRATA.

These errata are included in the consolidated list printed in the 1952 *Journal* Index issue.

Vol.	Page.	Line.	
1952	1427	10 *	*For* 1660 cm.$^{-1}$ *read* 817 cm.$^{-1}$.
	3374		Title and throughout the paper: *for* 2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid *read* 2 : 3-*seco*cholestane-2 : 3-dioic acid (similarly for its derivatives).
	4025	20	*After* 1-benzylaminonaphthalene *add* (23·3 g., 0·1 mol.).
	4090	5 *	*For* 35 *read* 40.
	4111		Table 2, *raise* (Va) *two lines*, i.e., *level with* [from degradation of (II)].
	4220	Table 1, No. 12.	} *For* 8-methyl *read* *N*-methyl.
	4225	7 (twice)	
	4522	12 *	*For* dianthronyl *read* dianthron-9-ylidene.
	4528	8 *	*For* carbon dioxide *read* carbon dioxide-free nitrogen.
	4567	20 *	*For* 75,000 *read* 7500.
			For 72,500 *read* 7250.
	4582	6 *	*For* 132—133° *read* 136—137°.
	4583	11	*For* N, 5·6% *read* *N*, 4·6%.
	4636		Table 2, the first italicized centre heading: for 4-(3-*Methylbenzothiazolin*-2-*ylidene*)-2-*thiazolid*-5-*ones* read 4-(3-*Methylbenzothiazolin*-2-*ylidene*)-2-*thiothiazolid*-5-*ones*.
	4701	15	*For* 4 : 9-diamino-2 : 6-diazapyrene *read* 4 : 9-diamino-2 : 7-diphenyl-1 : 6-diazapyrene.
	4754	26	For 2 : 4-*Dimethoxybenzyl* 2-*Hydroxy*-4 : 6-*dimethoxybenzyl Ketone* read 2 : 4-*Dimethoxybenzyl* 2-*Hydroxy*-4 : 6-*dimethoxyphenyl Ketone*.
	4755	27 *	*After* H, 6·2 *insert* ; 2OMe, 31·7.
		16 *	*For* 4-Ethoxy-2-methoxybenzoic acid (1 g.) *read* 4-Ethoxy-2-hydroxybenzoic acid (1 g.).
	4889	26 *	*For* $C_{31}H_{21}O_3$ *read* $C_{30}H_{30}O_3$.
	4890	6	*For* 3β-acetoxy-5α : 8α-epidioxyergost-9 : 22-ene *read* 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene.
		7	*For* uptake of 2 *read* uptake of 3.

* From bottom of page.

76. *Experiments on the Synthesis of Substances related to the Sterols. Part LI.* Completion of the Syntheses of Androgenic Hormones and of the Cholesterol Group of Sterols.*

By H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, Hugo Holtermann, and Sir Robert Robinson.

The formal total synthesis of *epi*androsterone has been completed. The first stage was transformation of Reich's tetradecahydro-1 : 7-diketo-2 : 13-dimethylphenanthrene (I), which had been synthesised by Cornforth and Robinson (*J.*, 1949, 1855), into Köster and Logemann's $\Delta^{9(14)}$-dodecahydro-7-hydroxy-1-keto-2 : 13-dimethylphenanthrene (XII; R = H). The latter was used as the first relay; † it was converted into ætio*allo*bilianic acid (X), which was securely characterised and then used, as the second relay, for conversion into *epi*androsterone (XXXIII; R = H). The conversion of this hormone into androstenedione had already been realised and, in order to bring in a further series of steroids, androstenedione has been changed into dehydroandrosterone. From the latter *allo*pregnanolone had already been obtained and this substance has been converted into cholestanol by way of a 17 : 20-dehydro-derivative. Manifold known transformations enable other members of the steroid group to be embraced in the synthetic scheme and examples are testosterone, cholesterol, vitamin D_3, and cortisone.

A preliminary account of the synthesis of *epi*androsterone has already been published (*Chem. and Ind.*, 1951, 389).

The complete synthesis of the tricyclic diketone (I) identical with a ketone obtained from the oxidative degradation of cholesterol and bile acids (Reich, *Helv. Chim. Acta*, 1945, **28**, 892) was described by Cornforth and Robinson (*Nature*, 1947, **160**, 173; Part XLVIII, *J.*, 1949, 1855) ‡ who foreshadowed that the further elaboration of substances containing the tetracyclic ring system of the steroids and male sex hormones might follow the lines adumbrated in earlier parts of this series (cf. Pedler Lecture, *J.*, 1936, 1087).

In fact several new methods for the construction of ring D were studied and will be discussed in a subsequent paper. Eventually, however, we decided to rely upon one of the earliest methods contemplated in this series, that involving a Reformatsky reaction for the construction of ring D.

The stages, with the exception of the first (II to III) are those described by Robinson and Walker (*J.*, 1938, 183) and Litvan and Robinson (*ibid.*, p. 1997), and used by Kuwada and Nakamura (*J. Pharm. Soc. Japan*, 1938, **58**, 235, 257) for the partial synthesis of dehydro*epi*androsterone (XI) from ætiobilienic acid (X) (stages VI to IX), by Bachmann, Cole, and Wilds (*J. Amer. Chem. Soc.*, 1940, **62**, 824) for the synthesis of equilenin (stages III to IX), and by Anner and Miescher (*Helv. Chim. Acta*, 1948, **31**, 2173) for the synthesis of œstrone (stages III to IX).

This route has the advantage that relay can be made from the tetracyclic ketone (IX) by oxidative ring fission; in addition, the appropriate ætiobilienic acid (X) of type (VI) can be isolated from the acid residues from the oxidation of cholesteryl acetate dibromide. Substantial quantities of this acid were obtained by the latter means, and its conversion into dehydro*epi*androsterone (XI; R = H) (Kuwada and Nakamura, *loc. cit.*; Hershberg, Schwenk, and Stahl, *Arch. Biochem.*, 1948, **19**, 300) was confirmed.

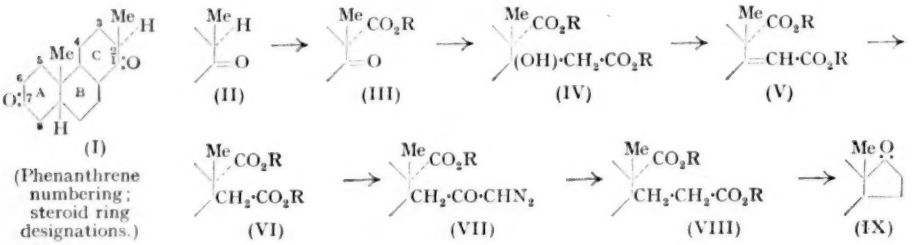
* Part L. *J.*, 1952, 1224.

† When, in a long synthesis, an intermediate is prepared by complete synthesis in small quantity and further supplies are drawn from natural sources or are derived from natural products, that intermediate may be described as a relay.

‡ The following errata occur in that paper (Part XLVIII):

p. 1846.	*For* Morton *read* Martin.
p. 1857, l. 5 from bottom.	*For* +33·5° *read* +38·5°.
p. 1863, l. 44.	*For* −33·5° *read* −38·5°.
p. 1864, ll. 8 & 9.	*For* 11·319 g. *and* 13·231 g. *read* 1·1319 g. and 1·3231 g.
l. 31.	*For* +9·3° *read* +9·8°.

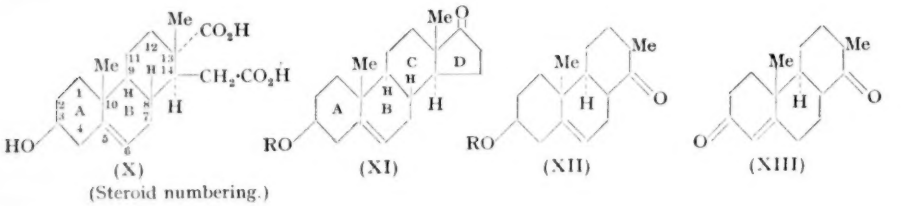
The most readily available tricyclic (ABC) substance which could stand in the direct line of our projected synthesis was clearly the hydroxy-ketone (XII; R = H), obtained as its acetate as a by-product of the oxidation of cholesteryl acetate dibromide by Köster and Logemann (*Ber.*, 1940, **73**, 299) and termed below the K.L. ketone; in view of its accessibility we decided to rely upon it as a relay. Its relation to (X) is obviously very



(I) (Phenanthrene numbering; steroid ring designations.)

close but consideration of later stages showed that it was unlikely that full advantage could be taken of this. And so it proved, since the double bond was perforce saturated in the course of our operations.

Another circumstance that made the decision to use K.L. ketone difficult was that the synthesis of the substance had not been accomplished although it had been converted into a synthetic tricyclic ketone, namely, the Reich diketone (I). Fortunately these doubts were soon dissipated by the brilliant work of Birch, and of Dauben, who indicated different methods for the conversion of cholestenone into cholesterol, a transformation which is a model for that required to bridge the gap between Reich diketone (I) and K.L. ketone (XII; R = H). As the work proceeded we became more and more committed to our selected, if not preferred, route, which was eventually carried to the end. The formal synthesis which we can now describe admits of many improvements and should be regarded as scaffolding.



(X) (Steroid numbering.)

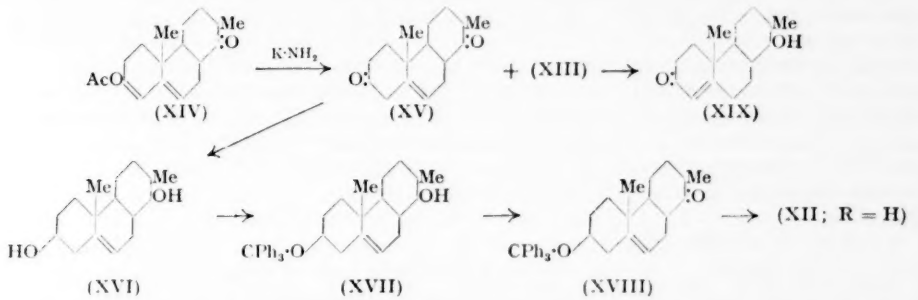
The following are the chief groups of stages. (1) Conversion of the Reich diketone (I) into the K.L. ketone (XII; R = H); (2) carboxylation of a derivative of the K.L. ketone; (3) synthesis of 3β-hydroxyætio*allo*bilianic acid from the end-product of (2); (4) conversion of the ætio*allo*bilianic acid into *epi*androsterone; (5) conversion of androstenedione into dehydro*epi*androsterone; and (6) synthesis of cholestanol from pregnenolone.

Stage (1).—Oppenauer oxidation of the K.L. ketone (XII; R = H) furnished the unsaturated diketone (XIII) from which Cornforth and Robinson (Part XLVIII, *loc. cit.*) obtained the Reich diketone (I). The latter was a product of degradation of deoxycholic acid by means of processes not involving the A : B ring fusion, which must therefore be of *cis*-decalin type. The method of preparation from (XIII) would also be expected to give the *cis*-decalin configuration on the grounds of numerous analogies, *e.g.*, the behaviour of cholestenone. Instances, however, are accumulating where the rule is not strictly observed, but in these there is usually a polar group in ring C or D, or its vicinity; and in the Experimental section we describe the catalytic reduction of androstenedione (XXXIV) which, contrary to earlier findings, gives the *cis*- and *trans*-decalin (A–B) derivatives in almost equal amount.

If, as seemed certain, the Reich diketone (I) is a *cis*-decalin (A–B), then it should be brominated in position 8 (phenanthrene) and afford (XIII) on dehydrobromination. Whilst we were studying these changes the processes were described by Billeter and Miescher (*Helv. Chim. Acta*, **1950**, **33**, 388). It remained to convert (XIII) into (XII) and we were greatly assisted by the publication of methods for the conversion of cholestenone into cholesterol (Birch, *J.*, **1950**, 2325; cf. Dauben and Eastham, *J. Amer. Chem. Soc.*, 1950, **72**, 2305; also Shoppee and Summers, *J.*, 1950, 687).

The ingenious methods of Birch, and of Shoppee and Summers, were followed in principle. It might be still better to use the more recently disclosed method of Dauben and Eastham (*J. Amer. Chem. Soc.*, **1951**, **73**, 4463) whereby a 75% yield of cholesterol is obtained by the reduction of the enol acetate of cholestenone with sodium borohydride.

Treatment of (XIII) with a mixture of acetyl chloride and acetic anhydride (cf. Inhoffen, *Ber.*, **1936**, **69**, 2144; Westphal, *Ber.*, 1937, **70**, 2128) gave the enol acetate (XIV) which was ammonolysed by means of potassamide in liquid ammonia, followed by ammonium chloride. The product was a mixture of recovered (XIII) with the new βγ-unsaturated ketone (XV). Attempts to isolate (XV) were defeated by its lability and hence the crude product was at once reduced by means of lithium aluminium hydride in ether. As a preliminary to the chromatographic separation of the reduction products we examined the reduction of K.L. ketone (XII) under similar conditions. Only one isomeride was produced and the reduction at position 1 (phenanthrene) was thus stereospecific. This implies the survival of the B–C *trans*-decalin system and also a particular orientation of the methyl and new *sec.*-alcoholic group in relation to it. Further comment on this matter is made below in connexion with the analogous results in the tetracyclic series.



We made use of the method of fractional elution of adsorbates (cf. Reichstein and Shoppee, *Discuss. Faraday Soc.*, **1949**, **7**, 305) and always employed activated alumina and material to be purified in the ratio 30 : 1, so that experience with the diol from K.L. ketone enabled us to look in the right place for the required stereoisomeride (XVI).

Available analogies made it clear that reduction at position 7 would probably take place in the two possible directions, though the desired isomeride should preponderate.

On reduction of the crude mixture of (XIII) and (XV) made by the ammonolysis of the enol acetate (XIV) we obtained the diol (XVI), identical with that furnished by reduction of K.L. ketone, together with the unsaturated diketone (XIII) and an unsaturated keto-alcohol (XIX) derived from (XIII). The keto-alcohol had the ultra-violet absorption of an αβ-unsaturated ketone.

The diol (XVI) isolated in this way was not quite homogeneous but it afforded a 7-triphenylmethyl ether (XVII) identical with the same derivative of the diol from the reduction of K.L. ketone.

This ether was prepared in order to protect the hydroxyl at position 7 after other devices (acetylation, hydrogen succinoylation, hydrogen phthaloylation) had been tried with unsatisfactory results.

The general idea was to assist the differential between positions 1 and 7 by using a sterically hindered substituent in the hope that the hindrance factors would be not merely

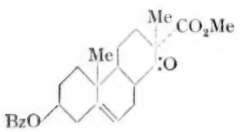
added but multiplied. Whether this was correct or not the method succeeded; on oxidation the ether (XVIII) of the K.L. ketone was obtained and by hydrolysis of this the K.L. ketone (XII; R = H) itself was produced.

In regard to the stereochemistry of this substance there can be no reason to suppose that the 3β-hydroxyl (7β- in XII) of cholesterol suffers inversion and similarly the B–C *trans*-ring fusion has surely survived. It is there in the first place and, even if it were not, the α-keto-group would induce its formation, the configuration at 9 (steroid; ≡ 12 phenanthrene) being assumed unalterable under usual circumstances. A doubt arises, however, in regard to the methyl group which is 13β in cholesterol.

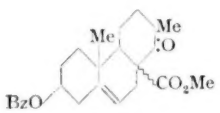
This could easily change to 13α (2α in the phenanthrene skeleton) under the influence of catalysts and the methyl is in the thermodynamically stable form because K.L. ketone is obtained by the hydrolysis of its acetate with methanolic potassium hydroxide. On the basis of Barton's reasoning (*Experientia*, **1950**, **316**; cf. Hassel, *Research*, **1950**, **504**), 2α being equatorially bound should be more stable than 2β (polar).

The formation of a single substance on reduction of K.L. ketone (see above) appears to support the 2β-configuration in which steric hindrance and tendency to produce equatorial bonds work in the same direction; whereas in the 2α-configuration they are opposed. Nevertheless it may very well be that one of these effects is predominant. In the case of the ketone, in the presence of powerful catalysts, the reversible processes should perhaps favour the emergence of the 2α-configuration. If the configuration of the new hydroxyl group could be ascertained by independent means it would throw light on the relative importance of the various factors which have been indicated.

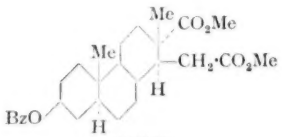
Stage (2).—A technique for the carboxylation of alicyclic ketones by treatment with sodium triphenylmethide in ether under nitrogen, followed by addition to carbon dioxide, was worked out. The product was carefully acidified and the carboxylic acid formed was extracted and esterified by diazomethane. An account of such model experiments with 2-methyl*cyclo*hexanone and *trans*-2-methyldecal-1-one will be submitted later. In the case of K.L. ketone the hydroxyl group was protected as benzoyloxy, so as to avoid the introduction of a new site of possible reactivity, such as the methyl of an acetoxy-derivative. Applying the method to K.L. ketone benzoate we obtained two isomeric keto-esters, separated by chromatography on alumina. These are designated (A) and (B) and were obtained in approximately the ratio 1 : 2 (A : B) (60—70%) yield.



(XX)



(XXI)



(XXII)

(A) is the more strongly adsorbed on alumina and assuming that (A) and (B) were stereoisomerides we concluded that (B) would be the isomeride required for our synthesis. It appeared to us that the *cis*-relation of polar groups, in this case BzO and CO_2Me, should tend to strong adsorption and we needed these groups in *trans*-relation. This argument was probably sound, given the premise, but it did not prove a reliable guide, and the outcome of our further work has been that (A) is certainly (XX), structurally and stereochemically the desired compound, whilst (B) is probably (XXI). The reasons for these conclusions are given below. As we only obtained a single stereoisomeride (XX) we were very fortunate to get the right one. This knowledge was acquired in a later phase of the work.

Stage (3).—The first attempt to carry out the stages (III to VI) with the keto-esters (A) and (B) was made in early days when the starting material available was exiguous.

The target was a derivative of ætio*allo*bilianic acid which Kuwada and Miyasaka (*J. Pharm. Soc. Japan*, **1936**, **56**, **631**) had already obtained by reduction of the accesssible ætiobilienic acid (X); we have examined some of the derivatives of the saturated acid. The dimethyl ester (XXII) of the *O*-benzoate crystallises well and exhibits a characteristic double melting point on the microscope hot-stage.

Selection of this objective implied that we would hydrogenate the 5 : 6-double bond (steroid numbering) in the course of the synthesis and thus increase the number of stages necessary in order to re-introduce it. This compromise was expedient in the first instance but there is no theoretical necessity for it and we hope to devise a method for the retention of the double bond through the course of the synthesis.

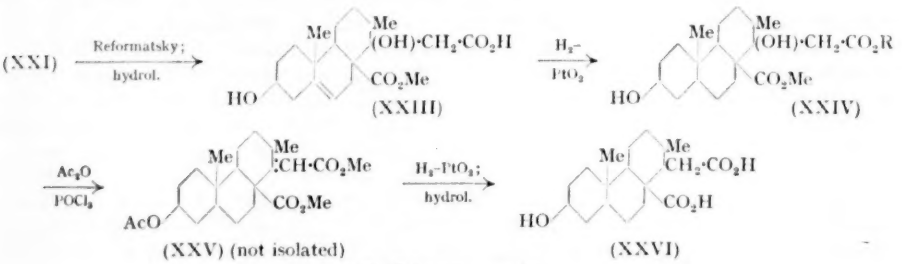
As we erroneously believed that (B) was the desired isomeride, (A) was used first. No attempts to isolate pure intermediates were made, and in the catalytic reduction the 14 : 15- and 5 : 6-double bonds (steroid numbering) were reduced together. The final products were isolated (by chromatography) as the 3-benzoate dimethyl esters. Four crystalline substances, (A) (i) m. p. 106—107°, (A) (ii) m. p. 153—155°, (A) (iii) m. p. 129—132°, $[\alpha]_D$ −11·5°, and (A) (iv) m. p. 121—123°, $[\alpha]_D$ +83·8°, were isolated in very small quantities (1—11 mg.). All these isomers appeared to be different from the natural methyl 3β-benzoyloxy-ætio*allo*bilianate (XXII), m. p. 144° and 158°, $[\alpha]_D$ −16·2° (but see below). The same series of reactions was then applied to the keto-ester (B). The overall yield was much lower. Chromatography of the benzoate dimethyl esters finally gave two crystalline substances, (B) (i) m. p. 148·5—149°, $[\alpha]_D$ +83°, and (B) (ii) m. p. 161—161·5°; both substances were different from the natural product.

As the isolation of four substances from the (A) series had suggested, contrary to general experience in the steroid field, that reduction of the 5 : 6-double bond was giving both *cis*- and *trans*-isomers (A–B linkage) it appeared possible that the desired compound was present in the (B) series, but had not been isolated owing to the small quantity of material available. Later we were able to dispose of adequate quantities of material as the result of generous gifts of residues from the oxidation of cholesteryl acetate dibromide and after the development of a simple method of isolation of K.L. ketone acetate from them. Preparation of suitable quantities of the A- and B-keto-esters was then undertaken and the later stages were re-investigated.

The Reformatsky reaction with methyl bromoacetate and the keto-ester (B) was first studied in detail. It was noted that appreciable debenzoylation occurred, which might account for the complex mixtures obtained in our earlier attempts to synthesise the ætio-*allo*bilianic acid derivative. The free 3-hydroxy-group would be partly removed, as well as the 14-hydroxy-group, in the dehydration. Accordingly the product was hydrolysed and isolated as the 3 : 14-dihydroxy half ester (XXIII, anticipating the argument given below). Attempts to convert the hydroxy-ester, after protection of the 3-hydroxy-group, *via* the 14-chloro-compound, into the bilienic acid were unsuccessful. Reduction of the 5 : 6-double bond was therefore performed before dehydration of the hydroxy-ester. These and subsequent steps are illustrated below. The following considerations had weight in the allocation of the structure (XXI) to the keto-ester-B. (i) The Reformatsky reaction gave a single stereoisomer; Anner and Miescher (*loc. cit.*) obtained approximately equal quantities of two stereoisomers in a similar reaction in the synthesis of œstrone. Similarly we obtained two steroisomers as products of the Reformatsky reaction applied to keto-ester-A. (ii) Hydrogenation of the crude unsaturated ester (XXV) gave substantially one product. Anner and Miescher obtained two isomers in equivalent quantities. (iii) The principal stereoisomeride (XXVI) finally isolated had a considerable positive rotation. (Another and still more dextrorotatory acid was isolated but the small quantity available did not enable us to establish its composition with certainty.) The last point is perhaps the most convincing. Fieser and Fieser ("Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, p. 214) have concluded from an analysis of optical rotatory data that in the natural steroids $C_{(13)}$ is a dextro- and $C_{(14)}$ is a lævo-rotatory centre of approximately equal power. 3β-Hydroxyætio*allo*bilianic acid 17-monomethyl ester had a specific rotation of −19°. The free acid would have practically the same rotation (cf. Heer and Miescher, *Helv. Chim. Acta*, 1947, **30**, 786). If the B-series is assumed to be epimeric at $C_{(13)}$ with the natural series, then even the more dextrorotatory ætio*allo*bilianic acid ($C_{(13)}$ −; $C_{(14)}$ +) of this series should have a negative rotation only slightly weaker than the "natural" acid, and this is in marked disagreement with the observed difference in rotation (ΔM_D 170) between the "natural" and the B-acids.

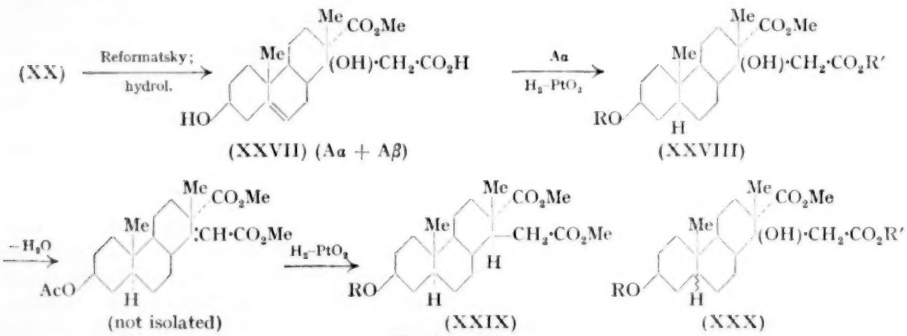
The rotations of the marrianolic and doisynolic acids (Fieser and Fieser, *op. cit.*, pp.

347—349) support these conclusions. It follows that isomer (B) cannot have a carbomethoxy-group at $C_{(13)}$ (steroid numbering). The alternative position is in the angle (XXI) and if this is so it is not surprising that the derivatives of the substance behave quite differently from those of the keto-ester used by Anner and Miescher (*loc. cit.*) in the synthesis of œstrone.



The B-keto-ester series.

The experience gained was now applied to the A-keto-ester series. After the Reformatsky reaction with methyl bromoacetate and mild hydrolysis of the product, two isomeric, lævorotatory dihydroxy half esters were obtained, namely Aα, m. p. 221° (XXVII) and Aβ, m. p. 182° (XXVII, inverted at $C_{(1)}$). When the Aα-hydroxy-ester was carried through the stages illustrated below, an oily dimethyl acetoxyætio*allo*bilianate was obtained. The crude product crystallised when seeded with the ester of natural origin. It was converted into the *O*-benzoate which was rigorously proved to be identical with the substance of natural origin. The specimens exhibited the characteristic double melting point, alone or mixed together, each had $[\alpha]_D$ −16·0°, and they were crystallographically identical. We are greatly indebted to Dr. D. M. Crowfoot Hodgkin for her invaluable co-operation throughout this research.



The Aα*-series.*

The Aβ-hydroxy-ester [XXVII, inverted at position 1 (phenanthrene)] was catalytically reduced to a dihydro-derivative (XXX; R = R′ = H). The related methyl ester acetate (XXX; R = Ac, R′ = Me) was not dehydrated under the conditions which succeeded in the Aα-series.

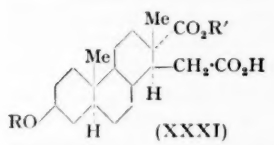
Two matters of more general interest emerge from these results. First, the K.L. ketone benzoate is carboxylated to some extent in the angle (position 11 of the phenanthrene ring) whereas 2-methyl-*trans*-decal-1-one was substituted in position 2 only. The chief difference between the tricyclic substance and its bicyclic model is the presence of the double bond in the former. This is in the βγ-position to the activated centre (γδ to carbonyl group) of the K.L. ketone benzoate and hence would not normally be regarded as exerting an electromeric effect. The reaction is quite normal in one sense because enolisation, or incipient enolisation, is possible on either side of the carbonyl group. The preference for one side or the other is a second-order phenomenon and may well be swayed by stereo-

chemical conditions determined to a sufficient extent by the presence or absence of the double bond. In addition, it is not out of the question that the double bond may exert its own direct polar effect on the activating system. This would be entirely analogous to very numerous secondary effects established in the study of the orientation of substitutions in aromatic compounds. The second point is that the carboxylation in both positions led to a single isomer in each case, or to a great preponderance of one isomer, if another substance was contained in the 30—40% not isolated. In the case of the (A) compound we know that the entering carboxyl is α-oriented. This could be due to the β-orientation of the neighbouring methyl group in position 2 (phenanthrene) which probably exists in the enolate ion. It is equivalent to assume that the bond-forming electrons on position 2, which may have a fractional value, are α-oriented. Such bond-forming electrons correspond to the displacements (a) in $^{-}O\overset{\curvearrowright a}{-}C\overset{\curvearrowright a}{=}CMe$· and there is reason to believe that a small value of (a) suffices to preserve the tetrahedral environment of the carbon atom, the electron or electron moiety functioning as the fourth group. These considerations do not solve the problem but they tend to put it one stage further back and it is beyond our present scope to pursue the matter further.

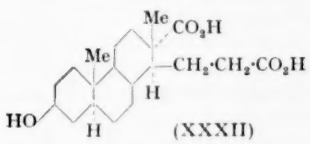
Summarising, the evidence bearing on the orientation of the 2-methyl group in K.L. ketone is conflicting. The theoretical argument, based on the influence of steric factors on stability, favours the α-configuration but two reactions (reduction and carboxylation), also discussed from a speculative theoretical angle, favour the β-configuration. Not one of these arguments is conclusive.

The question of the configuration of the B-keto-ester also remains open. Reasoning on stereochemical grounds leads to the conclusion that in this case also the carbomethoxy-group should be α-oriented.

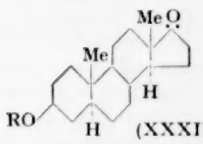
Stage (4).—The dimethyl ætio*allo*bilianate benzoate (XXII) was hydrolysed by methanolic potassium hydroxide to a hydroxy half-ester (XXXI; R = H, R′ = Me) which afforded an acetoxy half-ester (XXXI; R = Ac, R′ = Me) on acetylation. This acid was then homologated and carried through the stages (VI to IX) by the Arndt–Eistert and Blanc



(XXXI)



(XXXII)



(XXXIII)

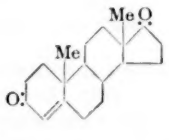
methods. Successive treatment of (XXXI; R = Ac) with oxalyl chloride, diazomethane, ammoniacal silver nitrate in aqueous ethanol, and boiling methanolic potassium hydroxide (16 hours) gave the partly crystalline homo-acid (XXXII). This was not further examined but was heated with acetic anhydride, and the acetate-anhydride pyrolysed. *epi*Androsterone acetate (XXXIII; R = Ac) was produced and purified by distillation and subsequent chromatography. The specimen (m. p. 103—104°; $[\alpha]_D$ +64·5° ± 2°) was identical in all respects with one made by catalytic hydrogenation and re-oxidation of dehydro*epi*androsterone acetate (m. p. 101·5—103·5°; $[\alpha]_D$ +68·5° ± 2°). As a punctilio *epi*androsterone was prepared by hydrolysis of its acetate.

Walden inversion at position 3 of *epi*androsterone leads to androsterone (Marker, Whitmore, Kamm, Oakwood, and Blatterman, *J. Amer. Chem. Soc.*, 1936, **58**, 338), from which 2-bromoandrostanedione, androstenedione, and testosterone have been obtained (Ruzicka, Plattner, and Aeschbacher, *Helv. Chim. Acta*, 1938, **21**, 866). The formation of androstenedione involves an abnormal dehydrobromination and a more straightforward method has recently been disclosed (Rosenkranz, Mancera, Gates, and Djerassi, *J. Amer. Chem. Soc.*, 1950, **72**, 4077). In this process the 2 : 4-dibromo-ketone is treated with sodium iodide to form the 2-bromo-4-iodo-derivative. Heating the latter with collidine affords the desired Δ^4-ketone by simultaneous dehydrobromination and de-iodination; alternatively these processes can be carried out successively.

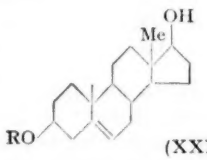
It should be noted that Marker and Rohrmann (*ibid.*, 1939, **61**, 2722) have prepared

ætiobilianic acid (A–B *cis*) by oxidative degradation of sarsasapogenin and have converted the acid (*ibid.*, 1940, **62**, 900) into 3β-hydroxyætiocholan-17-one, its 3β-epimeride, and testosterone. It might have been feasible to set up a *cis*-A–B series leading to ætiobilianic acid but this was not necessary since androstenedione (XXXIV) has been found to yield almost equal amounts of ætio- and ætio*allo*-cholane-3 : 17-dione on catalytic hydrogenation.

Stage (5).—In order to use dehydro*epi*androsterone (XI) as a relay, it was necessary to obtain it from androstenedione and this is the ring-homologue of the problem of converting (XIII) into (XII).



(XXXIV)



(XXXV)

The methods employed were the same as those used in Stage (1). The enol acetate of androst-4-ene-3 : 17-dione (Ruzicka and Fischer, *Helv. Chim. Acta*, 1936, **19**, 1371) was ammonolysed with potassamide in liquid ammonia, the solution acidified with ammonium chloride, and the products reduced with lithium aluminium hydride. We isolated unchanged androstenedione, testosterone, and androst-5-en-3β : 17β-diol (XXXV; R = H).

The diol was converted into dehydro*epi*androsterone by the 3-triphenylmethyl ether method, the various stages being parallel with those used in the tricyclic series. The final product was identical in all respects with authentic dehydro*epi*androsterone.

We take this opportunity to comment briefly on the mechanism of reduction by lithium aluminium hydride. The course of the reduction of carbonyl groups taken in the steroid series has been carefully studied by a number of workers and views concerning the mechanism have been advanced (Shoppee and Summers, *loc. cit.*, Trevoy and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675; Kenner and Murray, *J.*, 1950, 406; Brown, "Organic Reactions," Wiley, Vol. VI, p. 471; cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 173). At this date it is a commonplace to state that the carbon atom of a carbonyl group is cationoid (or electrophilic) in the first phase of a reaction and it is also self-evident that the stereochemical effect of substituents will often determine the side of entry of the addenda. The only question which we now propose to discuss is the nature of these addenda.

Shoppee (*loc. cit.*) and others have assumed that these are Li^+ (or appearance of an electrovalent anionic change on oxygen) and AlH_4^-. However, the attack on the cationoid carbon atom by AlH_4^- can at best be a mere preliminary electrovalent connexion—any covalency formed must be between carbon and hydrogen. A more direct mechanism would clearly be the attachment of oxygen to aluminium and hydrogen to carbon.

Very instructive parallel reactions have been discovered by Ziegler and Gellert and their co-workers (cf. *Angew. Chemie*, 1952, **64**, 523) who find that ethylene and lithium aluminium hydride afford lithium tetraethylaluminium $LiAlEt_4$. This focuses attention on the >Al–H link, and in fact AlH_3 is much more reactive than $LiAlH_4$ and is converted by ethylene into triethylaluminium. This reaction, and similar reactions with other olefins of the form $CH_2{:}CRR'$, is reversible. It was already known (Meerwein, *J. pr. Chem.*, 1937, **147**, 226) that triethylaluminium reduces chloral with the formation of ethylene : $3CCl_3{\cdot}CHO + AlEt_3 \longrightarrow (CCl_3{\cdot}CH_2{\cdot}O)_3Al + 3C_2H_4$.

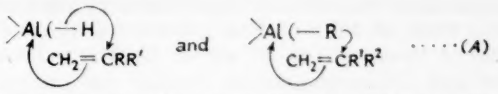
An important extension of the Ziegler reaction consists in the addition of olefins, $CH_2{:}CRR'$, to alkylaluminiums, a process which in the case of ethylene proceeds many times with formation of waxes (up to the present polythene analogues have not been so obtained). For example,

$$>Al{\cdot}CH_2{\cdot}CH_3 + CH_2{:}CH_2 \longrightarrow >Al{\cdot}Bu^n \xrightarrow{n C_2H_4} >Al{\cdot}[CH_2]_{2n}Bu^n$$

In the case of the higher olefins the Ziegler reaction follows the Markownikoff rule :

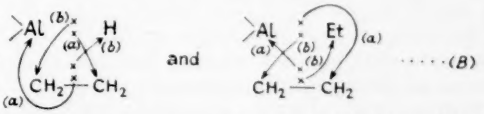
$$>Al{\cdot}Bu^n + CH_2{:}CHEt \longrightarrow >Al{\cdot}CH_2{\cdot}CHEtBu^n \rightleftharpoons >AlH + CH_2{:}CEtBu^n$$

Hence the mechanism is clearly either



(A)

or, preferably, corresponding mechanisms, travelling along the same lines in the first phases, but only involving transfer of one electron from the olefin to the aluminium atom, for example :



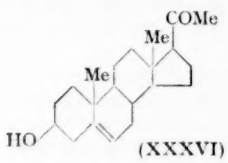
(B)

This essentially homopolar process is supposed to be *initiated* by the displacements (*a*)(*a*), which are followed by (*b*)(*b*). Any intermediate between the fully polar mechanism (*A*) and the homopolar mechanism (*B*) can be envisaged. In the case of the interaction of >AlH and >C=O we imagine there is a close approach to the (*A*) type, whereas that of >AlEt and CH_2:CH_2 is close to the (*B*) type.

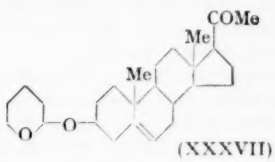
Such schemes in no way affect the validity of the conclusions respecting the influence of stereochemical conditions because these hold even if the larger group goes to oxygen. The determining circumstances are the direction of approach of the reagent and the location of electrons involved in the first stages of the addition.

Stage (6).—It was always our intention to use one of the androgenic hormones and its known transformation products as stepping stones to the cholesterol series, and the appropriate method has long been obvious. The submission of our preliminary note (*loc. cit.*) on the synthesis of the androgenic hormones was quickly followed by verbal disclosure of the very different syntheses by R. B. Woodward and his colleagues. A little later, a note was published (Woodward, Sondheimer, and Taub, *J. Amer. Chem. Soc.*, 1951, **73**, 3548) which anticipates our work in respect of the conversion of *allo*pregnanolone into cholestanol. However, we submit our own results in this field, because they are an integral part of the research initiated twenty years ago, and also because, up to the time of writing, the intermediate products have not been described.

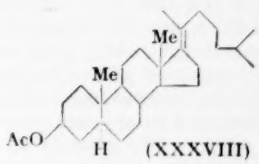
The chief reason for undertaking the reconversion of androstenedione into dehydro*epi*androsterone (see above) was to take advantage of the transformation of the latter hormone into 3-hydroxypregn-5-en-20-one (XXXVI) which had been accomplished by Butenandt and Schmidt-Thomé (*Ber.*, 1938, **71**, 1487; 1939, **72**, 182). A Grignard reaction with a suitably protected derivative of this substance was evidently the most convenient method for the introduction of the full sterol side-chain. As a preliminary we studied the methods available for the preparation of *iso*hexyl alcohol and submit a procedure which we regard as an improvement on all of them for the purpose in view. Unfortunately the reaction, neither of pregnenolone acetate, nor of the new dihydropyran adduct (XXXVII) of pregnenolone (cf. Woods and Kremer, *J. Amer. Chem. Soc.*, 1949, **71**, 1840; Greenhalgh, Henbest, and Jones, *J.*, 1950, 1190) with *iso*hexylmagnesium bromide gave satisfactory results. [(XXXVII) was crystalline in spite of the introduction of a new asymmetric centre, but no attempt was made to separate stereoisomerides.]



(XXXVI)



(XXXVII)



(XXXVIII)

In view of the abortive nature of these experiments only an outline of the reaction sequence is included in the Experimental section. The work had definite value to us in drawing attention to the character of the difficulties likely to be encountered, some of which were clearly due to the 5 : 6-double bond. As this could so easily be eliminated and as the

final product, namely, cholestanol, gives access to the whole cholesterol group, we turned to the case of *allo*pregnanolone (made from pregnenolone by Plattner, Heusser, and Angliker, *Helv. Chim. Acta*, 1946, **29**, 468; cf. Huang-Minlon, *J. Amer. Chem. Soc.*, 1949, **71**; 3301) and thus followed Woodward *et al.* (*loc. cit.*). The reaction between 3β-acetoxy*allo*pregnan-20-one and *iso*hexylmagnesium bromide was carried out in anisole, and the product dehydrated and acetylated (cf. Butenandt and Cobler, *Z. physiol. Chem.*, 1935, **234**, 218). Analysis and the infra-red spectrum of the pure product isolated by chromatographic procedures showed that it was 3β-acetoxycholest-17(20)-ene (XXXVIII).

This constitution applies to the 8% of solid isolated (absorption band at 12 μ absent) but the oily part of the material may have contained $\Delta^{20(21)}$- or $\Delta^{20(22)}$-isomerides. This was to be expected from the work of Reichstein and Koechlin (*Helv. Chim. Acta*, 1944, **27**, 549) on the dehydration of 20-methyl*allo*pregnane-3β : 20-diol. Both the solid and the oily product were hydrogenated (PtO_2): the solid (XXXVIII) afforded cholestanyl acetate in moderately good yield, but the oil gave only a small amount of cholestanyl acetate and the major part remained oily and gave no digitonide. The cholestanyl acetate was rigorously compared with a specimen of natural origin and proved identical with it in all respects, including the crystallographic data. The further transformations of cholestanol to cholestanone, cholest-4-enone, and cholesterol, and many other substances are well known. The newer methods of Birch and of Dauben for the conversion of cholestenone into cholesterol are mentioned above.

Experimental

M. p.s are uncorrected. Petrol refers to light petroleum of b. p. 40—60°.

7-Acetoxy-$\Delta^{7:9(14)}$*-decahydro-1-keto-2 : 13-dimethylphenanthrene* (XIV).—A solution of Δ^8-dodecahydro-1 : 7-diketo-2 : 13-dimethylphenanthrene (XIII) (2·5 g.) in acetic anhydride (20 c.c.) and acetyl chloride (20 c.c.) was refluxed for 3 hours, then concentrated to 5 c.c., and, on cooling, *7-acetoxy-*$\Delta^{7:9(14)}$*-decahydro-1-keto-2 : 13-dimethylphenanthrene* (2·3 g.) crystallised. Recrystallisation from ethanol gave plates, m. p. 114°, $[\alpha]_D^{17}$ −133° (*c* 0·96 in EtOH) (Found : C, 75·1; H, 8·2. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·3%).

$\Delta^{9(14)}$*-Dodecahydro-1 : 7-dihydroxy-2 : 13-dimethylphenanthrene* (XVI).—(*a*) The above enol acetate (6·0 g.) in ether (120 c.c.) was added to potassamide (from 6·0 g. of potassium) in liquid ammonia (600 c.c.). After 1 hour ammonium chloride (12·0 g.) was added, the solution kept for an hour, and the ammonia evaporated off. The residue was extracted with ether (5 × 200 c.c.). Evaporation of a portion of this solution gave an oil whose negative rotation ($[\alpha]_D^{15}$ −33°) (*c* 0·9 in EtOH) showed that it consisted largely of the βγ-unsaturated ketone.

The ethereal solution of the unsaturated diketones was added slowly to a solution of lithium aluminium hydride (4·0 g.) in ether (200 c.c.). After 2 hours the mixture was cooled in ice, and the excess of lithium aluminium hydride decomposed by the addition of 20% hydrochloric acid. The ethereal layer was washed with sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). The solvent was removed yielding an oil (4·4 g.) which was chromatographed in benzene (100 c.c.) on an alumina (50 g.) column, prepared in benzene. Three main fractions were obtained, *viz.*, (i) (1·5 g.) eluted by benzene, (ii) (397 mg.) eluted by benzene–ether (4 : 1), and (iii) (310 mg.) eluted by benzene–ether (7 : 3—1 : 4). These fractions were rechromatographed as follows :

(i) In benzene–petrol (2 : 3; 100 c.c.) on alumina (30 g.). The fraction eluted by benzene–petrol (1 : 1) yielded a white solid crystallising from ether in needles, m. p. 135—136°, $[\alpha]_D^{22}$ +116° (*c* 1·49 in EtOH) (Found: C, 77·6; H, 8·8. Calc. for $C_{16}H_{22}O_2$: C, 78·0; H, 8·9%). The m. p. was not depressed on admixture with Δ^8-dodecahydro-1 : 7-diketo-2 : 13-dimethylphenanthrene (XIII), m. p. 140°, $[\alpha]_D$ +128° in $CHCl_3$.

Fraction (ii) proved homogeneous, crystallising from ether in triangular prisms, m. p. 142°, $[\alpha]_D^{22}$ +85° (*c* 0·965 in EtOH). The ultra-violet absorption ($\lambda_{max.}$ 240 mμ, log $\varepsilon_{max.}$ 4·2) was characteristic of an αβ-unsaturated ketone (Found : C, 77·1; H, 9·3. $C_{16}H_{24}O_2$ requires C, 77·4; H, 9·6%). The product is therefore Δ^8*-dodecahydro-1-hydroxy-7-keto-2 : 13-dimethylphenanthrene* (XIX).

(iii) In benzene (20 c.c.) on alumina (9 g.). The fraction eluted by benzene–ether (7 : 3) yielded a white solid crystallising from ether in rosettes of needles, m. p. (capillary) 169—174° with softening from 120°, $[\alpha]_D^{20}$ −71° (*c* 1·09 in EtOH) (Found : C, 76·5; H, 10·4. $C_{16}H_{26}O_2$ requires C, 76·8; H, 10·4%). On the microscope hot-stage the needles started to sublime at

120°. The sublimate condensed in fronds of needles on the cover-slip. At 165—174° the needles contracted and changed into rods, the rods finally melting at 183°. The same phenomena were observed with a specimen made by the reduction of K.L. ketone (see below) or when the specimens were mixed. This substance is the *diol* (XVI) named in the heading of this section.

(*b*) The K.L. ketone (2·5 g.) in ether (250 c.c.) was added slowly to an ice-cold solution of lithium aluminium hydride (1·0 g.) in ether (100 c.c.), and the mixture set aside at the room temperature for an hour. The excess of lithium aluminium hydride was decomposed by the addition of 5% hydrochloric acid. The ethereal layer was washed with sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). The solvent was removed and the product (1·5 g.) crystallised from ether in fine needles, m. p. 183°, showing the polymorphic changes on heating described under (*a*, iii) and $[\alpha]_D^{16}$ −70° (Found : C, 76·1; H, 10·3%). Fractional crystallisation of the diol, or of its dihydrogen disuccinate followed by hydrolysis, gave no indication of the presence of an isomeride.

$\Delta^{9(14)}$-*Dodecahydro*-2 : 13-*dimethylphenanthr*-1 : 7-*ylene Dihydrogen Disuccinate*.—Dodecahydrodihydroxydimethylphenanthrene (1·0 g.) and succinic anhydride (1·0 g.) were heated with pyridine at 120° for 2 hours. The product was dissolved in ether (100 c.c.), washed with 20% hydrochloric acid until free from pyridine, then with water, and dried. The solvent was removed, and the product set aside in ether (5 c.c.) to crystallise. The derivative (50 mg.) was recrystallised from ether and obtained in needles, m. p. 154°, $[\alpha]_D^{16}$ −32° (*c* 1·3 in EtOH) (Found : C, 64·2; H, 7·4. $C_{24}H_{34}O_8$ requires C, 64·0; H, 7·6%). Further crops (200 mg.) were obtained from the mother-liquors but evaporation of the solvent gave an oily residue. Hydrolysis of the above *dihydrogen disuccinate* (130 mg.) with hot aqueous potassium hydroxide (5 c.c. of 3%) for 15 minutes gave the pure diol.

$\Delta^{9(14)}$-*Dodecahydro*-1-*keto*-2 : 13-*dimethylphenanthr*-7-*yl Hydrogen Succinate*.—The K.L. ketone (1·0 g.), succinic anhydride (1·0 g.), and pyridine (2 c.c.) was heated at 120° for 2 hours. The product was dissolved in ether, and washed with 20% hydrochloric acid till free from pyridine, and with water. The dried ethereal solution was concentrated to 10 c.c. and cooled, whereupon the *hydrogen succinate* (1·1 g.) crystallised in plates, m. p. 151—152°, $[\alpha]_D^{16}$ −57° (*c* 1·15 in EtOH) (Found : C, 69·0; H, 8·3. $C_{20}H_{28}O_5$ requires C, 69·0; H, 8·0%). Hydrolysis of the succinate by 5% aqueous potassium hydroxide yielded the theoretical quantity of the keto-alcohol.

$\Delta^{9(14)}$-*Dodecahydro*-1-*keto*-2 : 13-*dimethyl*-7-*triphenylmethoxyphenanthrene* (XVIII).—(*A*) The diol (XVI) (1·5 g.) and triphenylmethyl chloride (1·7 g.) in pyridine (5 c.c.) were heated on the steam-bath for 4 hours. The product was dissolved in ether and washed with 20% hydrochloric acid, with sodium hydrogen carbonate solution, then with water, and dried. Removal of the ether left a dark oil containing a few crystals. The oil was dissolved in benzene–petrol (300 c.c.; 1 : 4) and purified by chromatography on an alumina column (90 g.) prepared in petrol. Two main fractions were obtained; the first (623 mg.) was eluted by benzene–petrol (400 c.c., 1 : 4), and the second (313 mg.) by benzene–petrol (100 c.c., 2 : 3). The former was a waxy solid of indeterminate m. p. which was not purified by further chromatography, and was probably a mixture of the isomeric 1- and 7-ethers. It was oxidised as described below. On further purification by chromatography on alumina (10 g.) the second fraction, m. p. 135—145°, yielded triphenylmethanol, m. p. and mixed m. p. with an authentic specimen, 160°.

The waxy mixture of ethers (0·43 g.) was heated in toluene (15 c.c.) and *cyclo*hexanone (2 c.c.) to the b. p. Aluminium *iso*propoxide (0·2 g.) in toluene (5 c.c.) was added, and the solution was refluxed for 1½ hours and then distilled in steam. The residue was acidified with dilute hydrochloric acid, and the product isolated by means of ether. The oil (310 mg.), in benzene–petrol (20 c.c.; 2 : 3), was purified by chromatography on alumina (6·5 g.) prepared in the same solvent. The fraction eluted by benzene–petrol (80 c.c.; 1 : 1) on crystallisation from ether gave the $\Delta^{9(14)}$-*dodecahydro*-1-*keto*-2 : 13-*dimethyl*-7-*triphenylmethoxyphenanthrene*, m. p. 168—170°, $[\alpha]_D^{20}$ −66° (*c*, 2·6 in $CHCl_3$) (Found : C, 85·2; H, 7·8. $C_{35}H_{38}O_2$ requires C, 85·7; H, 7·8%). The m. p. was undepressed on admixture with an authentic specimen prepared by the reduction of the K.L. ketone triphenylmethyl ether (see below). Dr. D. Crowfoot Hodgkin and Dr. P. M. Cowan kindly carried out experiments on the *X*-ray diffraction patterns (powder photographs) of the two substances, and reported that they were identical.

(*B*) The K.L. ketone (330 mg.) and triphenylmethyl chloride (375 mg., 1 mol.) were heated in pyridine (1 c.c.) on the steam-bath for 4 hours. The product was isolated in the usual manner and chromatographed in benzene–petrol (10 c.c.; 1 : 1) on alumina (10 g.) prepared in benzene–petrol (2 : 3). The second fraction eluted by benzene–petrol (10 c.c.; 1 : 1) gave a white solid (200 mg.) crystallising from ether in plates, m. p. 160—164°, and the third fraction a further 100

mg. The fractions were combined and purified by chromatography, the triphenylmethoxy-ketone being obtained from benzene or ether in transparent plates, m. p. 168—170°, $[\alpha]_D^{17}$ −54° (*c* 1·19 in $CHCl_3$) (Found : C, 85·5, 86·4; H, 8·6, 7·9. $C_{35}H_{38}O_2$ requires C, 85·7; H, 7·8%). In later experiments repeated chromatography and crystallisation raised the m. p. to 176°.

$\Delta^{9(14)}$-*Dodecahydro*-1-*hydroxy*-2 : 13-*dimethyl*-7-*triphenylmethoxyphenanthrene* (XVII).—The above triphenylmethoxy-ketone (200 mg.) in ether (10 c.c.) was added to lithium aluminium hydride (100 mg.) in ether (250 c.c.), kept for an hour, and worked up as usual. The crystalline *product* (200 mg.) was chromatographed in benzene–petrol (20 c.c.; 1 : 9) on an alumina column (6 g.) prepared in petrol, and eluted by benzene–petrol (1 : 4). It was chromatographed once more, and crystallised from petrol in transparent plates, m. p. 80—81°, $[\alpha]_D^{17}$ −3° (*c* 1·07 in $CHCl_3$) (Found : C, 87·6, 87·9, 86·8; H, 6·5, 7·1, 6·5. $C_{35}H_{40}O_2$ requires C, 85·4; H, 8·1%). These results may be explicable on the grounds that the material is a molecular compound of the ether with triphenylmethane.

Attempts to repeat this experiment furnished the monoether as an oil which could not be crystallised but was directly oxidised to the ether of the hydroxy-ketone. To a boiling solution of the oily mono(triphenylmethyl) ether of the diol (XVI) (450 mg.) in toluene (15 c.c.) and *cyclo*hexanone (2 c.c.), aluminium *iso*propoxide (300 mg.) in toluene (15 c.c.) was added. The mixture was refluxed for 3 hours and distilled in steam. The oily product (200 mg.), isolated as usual, was purified by chromatography on alumina (6 g.) prepared in petrol. The fraction eluted by benzene–petrol (2 : 3) crystallised from petrol in rods, m. p. 120—135°. These were dissolved in benzene–petrol (1 : 4) and again purified by chromatography on an alumina column (5 g.) prepared in petrol. The fraction eluted by benzene–petrol (20 c.c.; 2 : 3) yielded the triphenylmethyl ether of the K.L. ketone which crystallised from petrol in rods, m. p. 170—172° (20 mg.). The mixed m. p. with an authentic specimen (m. p. 176°) was 170—172°.

$\Delta^{9(14)}$-*Dodecahydro*-7-*hydroxy*-1-*keto*-2 : 13-*dimethylphenanthrene* (K.L. *Ketone*) (XII).—$\Delta^{9(14)}$-Dodecahydro-1-keto-2 : 13-dimethyl-7-triphenylmethoxyphenanthrene (750 mg.) in chloroform (20 c.c.), cooled in ice and hydrochloric acid, was treated with an ice-cold saturated solution of hydrogen chloride in chloroform (50 c.c.). The mixture was kept at the room temperature for 30 minutes, washed with sodium hydrogen carbonate solution, then with water, and dried and the solvent removed. The product was chromatographed in benzene–petrol (100 c.c.; 3 : 7) on alumina (20 g.) prepared in petrol. The fractions eluted by benzene–petrol (2 : 3 and 1 : 1) yielded triphenylmethanol (351 mg.), m. p. 160°, and that eluted by benzene–petrol (7 : 3) yielded dodecahydrohydroxyketodimethylphenanthrene (110 mg.), m. p. 131—132°, $[\alpha]_D^{20}$ −87° (*c* 1·82 in $CHCl_3$); the m. p. was not depressed on admixture with authentic K.L. ketone, m. p. 133—134°, $[\alpha]_D^{20}$ −88°.

Isolation of Ketones from Residues from the Oxidation of Cholesteryl Acetate Dibromide.—Materials. British Drug Houses Ltd. divide the material obtained on treatment of the neutral fraction with semicarbazide into three crops. Crop 1 contains the majority of the dehydro*epi*-androsterone acetate semicarbazone. Crop 2 contains mixed semicarbazone. Crop 3, which is obtained by dilution of the mother-liquors from Crop 2 with water, concentration to small bulk, and absorption of the resulting oil on kieselguhr, does not contain an appreciable quantity of semicarbazones. 12 Kg. of Crop 2 and 17 kg. of Crop 3 were kindly supplied by British Drug Houses Ltd. In addition Dr. Hershberg of the American Schering Corporation kindly provided 5 kg. of residues which appeared to be very similar to B.D.H. Crop 2 residues. 2 Kg. of Crop 2 were examined in detail by a laborious process which is only outlined below. The tricyclic ketone thus isolated (15 g.) was used for the initial attempt to prepare the bilianic acids. The remainder of Crop 2 was not worked up in the same manner because a simple process for the isolation of the tricyclic ketone from Crop 3 was developed. This simple process could, with minor modifications, be applied to Crop 2. The material from Crop 3 was used for the second and successful attempt to prepare the bilianic acids.

Crop 2. A brief examination revealed that the tricyclic hydroxy-ketone (XII) of Köster and Logemann (*loc. cit.*) was not present as a semicarbazone. The dry residues were therefore continuously extracted with hot petrol. The extract was evaporated and the resulting mixture of acetates and lactones was hydrolysed with methanolic potassium hydroxide. The recovered neutral moiety, now lactone free, was triturated with ether, leaving relatively large quantities of cholesterol. The ether-soluble oil (190 g. from 2 kg. of residues) was dissolved in benzene (800 c.c.) and diluted with petrol (800 c.c.). This solution in two equal portions was passed through two alumina columns (1 kg. each) which were successively eluted with petrol, benzene, and chloroform, over 200 l. of solvents being used in all. Benzene–chloroform (7 : 1) eluted most of the desired K.L. ketone, contaminated with appreciable quantities of cholesterol. The

K.L. ketone was purified by conversion into the acetate and crystallisation from methanol. The total yield of K.L. ketone acetate was 14 g.

The process will, it is hoped, be described in greater detail in connexion with the description by one of us (H. H.) of the isolation of norcholesterolone (Ruzicka, Werner, and Fischer, *Helv. Chim. Acta*, 1937, **20**, 1291) from eluate-V (benzene–chloroform) and of a hydroxycholesterol from eluates-VI and -VII (benzene–chloroform). The latter substance crystallised from methanol in slender needles, m. p. 177—178·5° (Found: C, 80·7; H, 11·3. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%). Its *dibenzoate*, crystallised several times from ethanol, formed leaflets, m. p. 129—131° (Found: C, 81·0; H, 8·8. $C_{41}H_{54}O_4$ requires C, 80·6; H, 8·9%). This hydroxycholesterol is probably identical with a substance, m. p. 177°, of unknown constitution described by Windaus, Bursian, and Riemann (*Z. physiol. Chem.*, 1941, **271**, 177).

The semicarbazone fraction of Crop 2 was also examined in detail. It contained no tricyclic ketone, and the examination revealed no ketonic products other than those already isolated by other workers (Fieser and Fieser, "Natural Products related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, pp. 364—367). It was observed, during this work, that norcholesterol-24-one reacted quantitatively with Girard reagent-P in hot ethanol during 15 minutes. Under the same conditions pregnenolone was partly converted into a Girard derivative whilst dehydro*epi*androsterone was unaffected. The K.L. ketone acetate was unaffected even in the presence of naphthalene-β-sulphonic acid, and with continuous removal of water by azeotropic distillation with benzene–ethanol.

Crop 3. This product contained no semicarbazones and unlike Crop 2 consisted largely of 3-hydroxy(not 3-acetoxy)-compounds. The free-flowing powder (750 g.) was extracted with boiling methanol (2 l.), and the solution filtered from kieselguhr. On cooling, large quantities of crude cholesterol separated. The filtrate was treated with cold methanol (2 l.) containing potassium hydroxide (100 g.). After 48 hours a further crop of cholesterol was collected. The filtrate was then concentrated to a small bulk under reduced pressure on the steam-bath and the residue was shaken continuously with ether and water. The aqueous layer on acidification, extraction with chloroform, refluxing of the chloroform solution for 1 hour, and extraction with aqueous sodium carbonate gave a chloroformic solution of lactones. Removal of lactones by this alkaline hydrolysis was found to be essential for the subsequent smooth distillation of ketones. The ethereal extract was freed from solvent, and the residual oil was acetylated with acetic anhydride–pyridine in the usual manner. The mixture of acetoxy-compounds was isolated by ether and heated to 140—150° and the vacuum was progressively applied until there was no frothing at 0·1 mm. The hot oil was rapidly transferred to a 500-c.c. glass retort packed with glass wool, and the retort was connected to a receiver and mercury-vapour pump by all-glass joints; full vacuum was then rapidly applied. Unless the oil was still quite mobile, inconvenient frothing occurred. The retort was then heated in an air-bath, which completely enclosed the distillation bend, to 170°/0·001 mm. for 6 hours; the golden distillate partly solidified. One or two crystallisations from methanol gave pure K.L. ketone acetate, m. p. 126—127°. 17 Kg. of Crop 3 residues, worked up in this manner, gave approx. 200 g. of this ketone.

Redistillation of the volatile material collected in the cold traps during the distillation of K.L. ketone acetate (in the hope that some products of profound degradation of the sterol nucleus might be obtained) gave fine elongated plates or needles (subliming readily at 50°/0·001 mm.). The substance crystallised readily from petrol, had m. p. 78—80°, and proved to be acetamide.

Carboxylation of 7-*Benzoyloxy*-$\Delta^{9(11)}$-*dodecahydro*-1-*keto*-2 : 13-*dimethylphenanthrene*.—The K.L. ketone acetate did not react appreciably with 2 : 4-dinitrophenylhydrazone in aqueous-alcoholic hydrochloric acid during 0·5 min. at the b. p. The ketone appears to yield a digitonide which formed colourless needles but these were not closely examined.

The K.L. ketone was prepared from its acetate by hydrolysis with 5% methanolic potassium hydroxide at the room temperature for 4 days. The hydroxy-ketone was usually isolated by means of ether (solution dried over $MgSO_4$) and directly benzoylated.

The *benzoate* was prepared from the K.L. ketone by pyridine–benzoyl chloride at room temperature. It crystallised from ethanol in colourless prisms, m. p. 155—156°, $[\alpha]_D^{20}$ −39·6° (*c* 1 in $CHCl_3$) (Found: C, 78·6; H, 8·0. $C_{23}H_{28}O_3$ requires C, 78·4; H, 8·0%).

Into a solution of the K.L. ketone benzoate (4·0 g.) in dry benzene (40 c.c.), in a separatory funnel, a solution of sodium triphenylmethide in ether was transferred under pressure of nitrogen until a faint pink colour persisted. The suspension of the sodium enolates was then run on chopped solid carbon dioxide. After 10 mins., distilled water was added and the mixture was shaken mechanically The benzene layer was extracted three times with ice-cold 2N-sodium

hydroxide (if emulsions were formed the mixture was acidified and extracted again with aqueous sodium hydroxide). The combined ice-cold aqueous extracts were acidified with ice-cold 2N-hydrochloric acid and rapidly extracted with ether. The ethereal extract was then treated with an excess of ethereal diazomethane. After 0·5 hour the excess of diazomethane was decomposed with 2N-hydrochloric acid. The ethereal extract was washed with aqueous sodium hydrogen carbonate, and with water and dried ($MgSO_4$). On removal of the ether a white crystalline residue of keto-esters (3·0 g.) was obtained. The yield was considerably less when the experiment was scaled up (to 40 g. of K.L. ketone benzoate).

Separation of Methyl 7-Benzoyloxy-$\Delta^{9(14)}$*-dodecahydro-1-keto-2 : 13-dimethylphenanthrene-2-carboxylate* (XX) *and -11-carboxylate* (XXI). (*The A- and B-Keto-esters, respectively.*)—The mixed keto-esters (8·0 g.) were chromatographed in benzene (40 c.c.)–petrol (160 c.c.) on alumina (160 g.). The following fractions (eluant in parentheses) were obtained: (i) 0·15 g., m. p. 91—92°, triphenylmethane (benzene–petrol, 3 : 7); (ii) m. p. 141—147° (benzene–petrol, 1 : 1); (iii) 3·41 g., m. p. 147—148° (benzene); (iv) oil (benzene); (v) 1·91 g., m. p. 177—179° (benzene–chloroform, 7 : 3); (vi) oil (chloroform). Fractions (ii), (iv), and (vi) were rechromatographed, giving the following fractions: (*a*) 0·24 g., m. p. 160—177° (benzene–petrol, 3 : 7); (*b*) 75 mg. (benzene–petrol, 3 : 7); (*c*) 1·02 g., m. p. 146—148° (benzene–petrol, 7 : 3); (*d*) 0·1 g., m. p. 105—148° (benzene); (*e*) m. p. 153—155° (benzene–chloroform, 9 : 1); (*f*) 74 mg., m. p. 177—179° (benzene–chloroform, 1 : 1). Fractions (iii) and (*c*) (4·43 g.) consisted of the B or 11-*carbomethoxy*-isomer (XXI), which crystallised from methanol in colourless, thick prisms, m. p. 148—149°, $[\alpha]_D$ −80° (*c* 1 in $CHCl_3$) (Found: C, 73·3; H, 7·3. $C_{25}H_{30}O_5$ requires C, 73·1; H, 7·3%). Fractions (v) and (*f*) (1·98 g.) consisted of the A or 2-*carbomethoxy*-isomer (XX), which crystallised from methanol in colourless needles, m. p. 177—179°, $[\alpha]_D$ −100° (*c* 1 in $CHCl_3$) (Found: C, 73·0; H, 7·3%). Fraction (*a*) after three recrystallisations from methanol had m. p. 183—185° and consisted of methyl triphenylacetate (Found: C, 83·0; H, 6·0. Calc. for $C_{21}H_{18}O_2$: C, 83·4; H, 6·0%). Fraction (*e*) did not depress the m. p. of a specimen of the starting material (K.L. ketone benzoate).

Attempted Preparation of the Bilianic Acids from Substance-A.—The keto-ester A (1·5 g.), activated zinc (4·5 g.), ether (2·5 c.c.), benzene (25 c.c.), and methyl bromoacetate (1·5 c.c.) were stirred and heated under nitrogen. On addition of a crystal of iodine a vigorous reaction was initiated. The mixture was stirred and refluxed for 24 hours with occasional addition of methyl bromoacetate (total 3·0 c.c.) and zinc (total 4·5 g.). The mixture was cooled in ice and shaken with ice-cold aqueous acetic acid. The organic layer was washed with cold dilute aqueous ammonia, and with water, and was dried ($MgSO_4$). The residue (1·68 g.) crystallised readily but only 0·2 g. of a pure isomer was obtained on three crystallisations from methanol; this formed colourless prisms, m. p. 164—165°, of *methyl 3-benzoyloxy-*$\Delta^{9(14)}$*-decahydro-1-hydroxy-2 : 13-dimethylphenanthrene-1-acetate-2-carboxylate* (Found: C, 69·2; H, 7·6. $C_{28}H_{36}O_7$ requires C, 69·4; H, 7·5%). The crude ester (1·6 g.) was dissolved in dry pyridine (16 c.c.); phosphoryl chloride (1·6 c.c.) was added with caution, and the mixture was refluxed gently for 45 minutes. The dark brown reaction mixture was cooled and poured on chopped ice. The mixture was shaken with ether and ice-cold 2N-hydrochloric acid. The ethereal layer was washed with more acid, and water, and dried ($MgSO_4$). On evaporation of the solvent a solid (1·12 g.) was obtained which crystallised from methanol as fine, white needles, m. p. 143—153° with sintering at 135°. This was assumed to be a mixture of geometrical isomerides of the unsaturated *benzoate dimethyl* ester (cf. V) (Found: C, 71·9; H, 7·6. $C_{28}H_{34}O_6$ requires C, 72·0; H, 7·3%).

The crude unsaturated esters (1·1 g.) were dissolved in 10% methanolic potassium hydroxide (10 c.c.), and the mixture was refluxed for 6 hours. After concentration *in vacuo*, water was added and neutral material was removed by ether-extraction. The acids, on acidification of the aqueous solution, were extracted with ether. The ethereal extract was treated with ethereal diazomethane. The resulting methyl esters (0·6 g.), freed from methyl benzoate at 110°/0·01 mm. during an hour, were hydrogenated in glacial acetic acid in the presence of platinic oxide. Analysis of the product after benzoylation suggested that hydrogenation was incomplete. The substance was therefore hydrolysed, esterified, hydrogenated, and re-benzoylated. The mixture of benzoate dimethyl esters (0·36 g.) was then chromatographed on acid-washed alumina. The fractions eluted with benzene–petrol (1 : 1) crystallised on slow evaporation of a light petroleum (b. p. 60—80°) solution. The product (70 mg.) was crystallised several times from light petroleum (b. p. 60—80°). *The benzoate dimethyl* ester (cf. VI) crystallised in elongated prisms, m. p. 106—107° (microscope hot-stage) (Found: C, 70·8; H, 7·4. $C_{28}H_{36}O_6$ requires C, 71·5; H, 8·1. $C_{28}H_{38}O_7$ requires C, 69·1; H, 7·8%). This sample was unfortunately lost before its specific rotation could be determined. The fraction eluted with benzene–petrol

(4 : 1) deposited a few crystals A (ii) on evaporation of the solvent. The substance, after one recrystallisation from light petroleum (b. p. 60—80°), melted at 153—155° (microscope hot-stage). There was insufficient material (<1 mg.) for rotation or analysis. A crystal on admixture with authentic natural bilianate showed a strong depression of the m. p. Two further isomers were isolated in such small quantities that a rotation or analysis could be determined but not both. The former only was determined. A(iii), crystallised in fine, hair-like needles from light petroleum (b. p. 60—80°), had m. p. (microscope hot-stage) 129—132°, $[\alpha]_D^{20}$ −11·5° (*c* 1 in $CHCl_3$). A(iv) crystallised from light petroleum (b. p. 60—80°) as colourless, imperfect prisms, m. p. 121—123° (microscope hot-stage), $[\alpha]_D^{20}$ +83·8° (*c* in $CHCl_3$).

Attempted Preparation of the Bilianic Acids from Substance-B.—The same procedure was used as for substance-A. The Reformatsky reaction proceeded less smoothly, and the dehydration was unsatisfactory. The benzoate dimethyl esters were finally purified by chromatography. The fraction eluted with methanol and crystallisation from light petroleum (b. p. 60—80°) gave colourless prisms (11 mg.), m. p. 148·5—149° (microscope hot-stage), $[\alpha]_D^{20}$ +83° (*c* 1 in $CHCl_3$) (Found : C, 71·7; H, 8·0. $C_{28}H_{36}O_6$ requires C, 71·5; H, 8·1%). The rotation alone was sufficient to indicate that this was not the *natural* bilianate. The fraction eluted with benzene eventually gave a few colourless, rectangular plates (<1 mg.), m. p. 161—161·5° (microscope hot-stage).

After a considerable interval these experiments were resumed.

11-*Carbomethoxy*-$\Delta^{9(14)}$-*dodecahydro*-1 : 7-*dihydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetic Acid* (XXIII).—A mixture of the B-keto-ester (2·001 g.), benzene (20 c.c.), ether (20 c.c.), granulated zinc (6 g.; activated according to Fieser and Johnson, *J. Amer. Chem. Soc.*, 1940, **62**, 576), coarsely ground Pyrex glass (15—20 g.; 20-mesh), and methyl bromoacetate (2 c.c.) was stirred and refluxed under nitrogen. Addition of iodine (0·2 g.) initiated the reaction; a sticky greenish solid was formed and adhered to the glass, leaving the zinc surface clean. After 8 hours, more methyl bromoacetate (0·75 c.c.) was added; after 10 hours, heating and stirring were stopped. Next day, ice-cold 2N-acetic acid (50 c.c.) was added, and the glass and residual zinc were removed and washed with dilute acetic acid and ether. The ether–benzene layer was washed with water and then four times with dilute, ice-cold aqueous ammonia; after a final washing with water it was dried ($MgSO_4$) and evaporated at low pressure, finally at 40°/0·5 mm. The residue was dissolved in a little methanol, seeded with the keto-ester, and left at 0° for 2 days with occasional shaking. Unchanged keto-ester (582 mg.) was removed and the filtrate evaporated, leaving a gum (1853 mg.) smelling of methyl benzoate. Hot methanol (88 c.c.) was added, followed gradually by 0·2N-sodium hydroxide (44 c.c.). The mixture was boiled for 19 hours, the methanol was largely removed at low pressure, and the residue after dilution with water was extracted with ether. The ethereal extract smelled strongly of acetophenone. Acidification of the aqueous solution, freed from ether, gave a crystalline precipitate (853 mg.), m. p. 188—192°. A small further quantity was obtained by extracting the filtrate with ether and removing benzoic acid from the crude acid by extraction with light petroleum. Recrystallisation from aqueous methanol gave the *half-ester* as slender needles, m. p. 195—196°, $[\alpha]_D^{20}$ −57° (*c* 3·3 in EtOH) (Found : C, 65·7; H, 8·2. $C_{20}H_{30}O_6$ requires C, 65·6; H, 8·2%). The mother-liquors were examined for a stereoisomer, but without result. The *methyl* ester, prepared with diazomethane in the usual manner, crystallised from ether in silky needles, m. p. 164—165°, $[\alpha]_D^{20}$ −57° (*c* 4·0 in $CHCl_3$) (Found : C, 65·7; H, 8·3. $C_{21}H_{32}O_6$ requires C, 66·3; H, 8·4%).

The half-ester (478 mg.) in acetic acid (5 c.c.; purified) with platinum oxide (63 mg.) was shaken with hydrogen at room temperature and pressure, one molecular proportion being absorbed in 15 minutes. Ethanol was added to redissolve the crystalline product, the catalyst was removed, and the solvent evaporated. Recrystallisation of the residue from acetone gave stout prisms, m. p. 216°, of 11-*carbomethoxyperhydro*-1 : 7-*dihydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetic acid* (XXIV; R = H) * (90%), $[\alpha]_D^{19}$ −15·8° (*c* 5·0 in EtOH) (Found : C, 65·1; H, 8·7. $C_{20}H_{32}O_6$ requires C, 65·2; H, 8·7%).

This product (500 mg.), dissolved in a little dioxan, was esterified with ethereal diazomethane. The *methyl* ester (XXIV; R = Me), crystallised from light petroleum (b. p. 60—80°) in silky needles (487 mg.), m. p. 132°, $[\alpha]_D^{19}$ −18·2° (*c* 2·6 in $CHCl_3$) (Found : C, 65·2; H, 8·9. $C_{21}H_{34}O_6$ requires C, 66·0; H, 8·9%). It was dissolved in dry pyridine (2 c.c.), and acetic anhydride (1 c.c.) added. After 20 hours at 37° the product, a gum, was isolated in the normal manner, dissolved in dry pyridine (5·5 c.c.), cooled in ice, and treated dropwise with freshly distilled phosphoryl chloride (0·55 c.c.). After 3 hours' refluxing the solution was cooled, poured on ice, acidified, and extracted with ether. Evaporation of the ether left a gum (470

mg.), $[\alpha]_D^{22}$ −45° (in MeOH). This was dissolved in pure ether and the solution passed through acid-washed alumina (5 g.). The filtrate was divided into two parts.

One half was evaporated, and the residue was hydrogenated in purified acetic acid (5 c.c.) at room temperature and pressure in presence of platinum oxide (60 mg.). After 48 hours the catalyst was removed and the solution, which showed $[\alpha]_D^{22}$ +8°, was evaporated. The residue was dissolved in methanol (12 c.c.) and neutralised; 0·2N-sodium hydroxide (7 c.c.) was then added and the mixture was refluxed overnight, The resulting acidic product (200 mg.) was isolated in the usual way; it deposited the undehydrated half-ester (XXIV; R = R′ = H) (marked * above) (31 mg.) when kept in ethyl acetate–light petroleum. The rest of the product (" residue X ") was saponified (see below).

The other half of the alumina filtrate was evaporated and the residue dehydrated again (3 hours' reflux) with pyridine (2·5 c.c.) and phosphoryl chloride (0·25 c.c.). The product was isolated as before, passed through alumina, and hydrogenated in acetic acid (5 c.c.), over platinum oxide (50 mg.), for 18 hours. The solution, $[\alpha]_D^{22}$ +13°, was evaporated and the residue in hexane was chromatographed on acid-washed alumina (20 g.), the effluents being examined polarimetrically. Hexane and hexane–benzene (3 : 1) eluted only a trace of material; with hexane–benzene (1 : 1), after a fore-run (31 mg.) of $[\alpha]_D^{22}$ +3° (these rotations are approximate), a gum (125 mg.) of +10° was obtained. After this, a fraction (34 mg.) of $[\alpha]_D^{22}$ +20° was slowly eluted; the column was then washed out with ether to give a final fraction, $[\alpha]_D^{22}$ +30° (37 mg.). After attempts to crystallise these " acetate dimethyl ester " fractions as such or after conversion into "hydroxy monomethyl ester," "hydroxy dimethyl ester," and "3 : 5-dinitrobenzoate dimethyl ester " had all failed, they were saponified to the " hydroxy-dicarboxylic acid " state, either by refluxing them overnight with 10% potassium hydroxide in methanol or by fusion for a few minutes with potassium hydroxide and water at 150—160°. The acids were isolated by means of ether and crystallised from aqueous acetic acid. From the +3° and +10° fractions, solvated *perhydro-7-hydroxy-2 : 13-dimethylphenanthrene-1-acetic-11-carboxylic acid* (XXVI) (~60 mg.) was obtained and recrystallised from acetic acid as well-formed prisms, m. p. about 140°, $[\alpha]_D^{20}$ +26·5° (*c* 4·67 in EtOH) (Found: C, 63·0; H, 8·5%; equiv., 132. $C_{19}H_{30}O_5,C_2H_4O_2$ requires C, 63·3; H, 8·5%; equiv., 133). Another, and perhaps unsolvated, form crystallised poorly from ethyl acetate, with m. p. 215°, $[\alpha]_D^{22}$ +33° (*c* 1 in MeOH); crystallisation of this from acetic acid gave the solvated form. From the +30° fraction another *acid* was obtained; it crystallised from ethyl acetate in small leaflets (2·5 mg.), m. p. 242°, $[\alpha]_D^{22}$ +72° (*c* 0·5 in $CHCl_3$); after recovery of the specimen from the rotation tube only 1·47 mg. were available for analysis (Found: C, 69·5; H, 8·7. $C_{19}H_{30}O_5$ requires C, 67·5; H, 8·9. $C_{19}H_{30}O_4$ requires C, 70·8; H, 9·3%). Accordingly this acid may lack the 7-hydroxy-group.

Saponification (by potassium hydroxide fusion) of " residue X " without chromatography, and crystallisation of the product from aqueous acetic acid, gave a first crop of the solvated acid, a second crop (6 mg.) consisting largely of the acid, m. p. 242° (2 mg. after recrystallisation from ethyl acetate), and further crops of the solvated acid (total about 60 mg.). The latter acid was also obtained from the residues of a previous experiment where dehydration had been far from complete and a considerable amount of undehydrated material had been separated as the acid.

2-Carbomethoxy-$\Delta^{9(14)}$-dodecahydro-1 : 7-dihydroxy-2 : 13-dimethylphenanthrene-1-acetic Acid α and β (XXVII).—A mixture of the A keto-ester (XX) (1·499 g.) with benzene (25 c.c.), ether (20 c.c.), methyl bromoacetate (1·5 c.c.), ground glass (15 g.), and activated zinc (4·5 g.) was heated and stirred under nitrogen, and reaction was initiated by addition of iodine (0·2 g.). The mixture was refluxed for 16 hours, methyl bromoacetate (1·5 c.c.) being added after 6 and 12 hours, and zinc (3·5 g.) after 12 hours. The total neutral product (1·967 g. after drying at 80°/1 mm.) was isolated as described above for the B series. It was dissolved in hot methanol (100 c.c.); 0·2N-sodium hydroxide (55 c.c.) was gradually added and the mixture was refluxed for 27 hours; a strong smell of acetophenone was noticed. Most of the methanol was removed at low pressure, and the residue was twice extracted with ether, freed from dissolved ether, brought to a volume of 120 c.c., and acidified. The oily precipitate was extracted several times with ether. The extract was treated with magnesium sulphate and a little charcoal, filtered, and evaporated. The residue was extracted repeatedly with hot petrol to remove benzoic acid, then dissolved in a little ether and cooled, whereupon *2-carbomethoxy-$\Delta^{9(14)}$-dodecahydro-1 : 7-dihydroxy-2 : 13-dimethylphenanthrene-1-acetic acid* α (240 mg.) separated. Recrystallisation from ethyl acetate gave colourless rods, m. p. 221°, $[\alpha]_D^{21}$ −50° (*c* 2·5 in MeOH) (Found, in material dried at 135° *in vacuo*: C, 65·5; H, 8·2. $C_{20}H_{30}O_6$ requires C, 65·6; H, 8·2%).

The ethereal filtrate from the α acid left a residue (966 mg.) which eventually crystallised but

could not easily be purified. Some of it (800 mg.) was esterified with ethereal diazomethane. The resulting crude ester was treated in a little benzene with pyridine (0·4 c.c.) and 3 : 5-dinitrobenzoyl chloride (0·8 g.). Next day the product was isolated by normal procedures; crystallisation from ethyl acetate gave two light yellow 3 : 5-*dinitrobenzoates* of methyl $\Delta^{9(14)}$-dodecahydro-1 : 7-dihydroxy-2 : 13-dimethylphenanthrene-2-carboxylate-1-acetate. The Aα derivative, prisms from ethyl acetate, had m. p. 187—188° (Found: C, 58·3; H, 6·0. $C_{28}H_{34}O_{11}N_2$ requires C, 58·5; H, 5·9%) undepressed by a specimen prepared from the Aα acid of m. p. 221°. The Aβ derivative separated from ethyl acetate in fine needles, m. p. 186—187° depressed by the Aα isomer (Found: C, 58·5; H, 5·7%). The Aβ ester was saponified with 0·4N-aqueous-methanolic sodium hydroxide, and dinitrobenzoic acid then removed by reduction with sodium dithionite. This was not a good procedure and the recovery of saponified product was poor. Recrystallisation from aqueous acetic acid gave hydrated 2-*carbomethoxy*-$\Delta^{9(14)}$-*dodecahydro*-1 : 7-*dihydroxy*-2 : 13-*methylphenanthrene*-1-*acetic acid* β in nodules, m. p. 182—183°, $[\alpha]_D^{22}$ −67° (*c* 2 in MeOH) (Found: C, 63·8; H, 7·8. $C_{20}H_{30}O_6,\frac{1}{2}H_2O$ requires C, 64·0; H, 8·3%).

2-*Carbomethoxyperhydro*-1 : 7-*dihydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetic Acid* α (XXVIII; R = R′ = H).—The above monomethyl ester α (127·6 mg.) was hydrogenated in acetic acid (5 c.c.) over platinum oxide (15 mg.). Uptake of hydrogen was rapid but shaking was continued for several hours. The catalyst and solvent were removed and the residue crystallised from aqueous acetic acid in fine needles (72 mg.). The *monomethyl ester* α (XXVIII; R = R′ = H) appeared to be solvated; it softened at 160°, resolidified, and melted at 192° (decomp.); it had $[\alpha]_D^{22}$ −8° (*c* 1·4 in MeOH) (Found, in material dried *in vacuo* at 80°: C, 62·2; H, 9·3. $C_{20}H_{32}O_6,H_2O$ requires C, 62·2; H, 8·8%). A further 25—30 mg. were obtained from the mother-liquors.

Methyl Perhydro-1 : 7-*dihydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetate*-2-*carboxylate* α (XXVIII; R = H, R′ = Me).—The monomethyl ester (XXVIII) above (95 mg.) was disso ved in a little methanol and esterified with ethereal diazomethane. The *dimethyl* ester (85 mg.) separated from light petroleum (b. p. 60—80°) in blades, pointed at one end, m. p. 141—142°, $[\alpha]_D^{22}$ −11·5° (*c* 1·6 in MeOH) (Found: C, 65·7; H, 9·0. $C_{21}H_{34}O_6$ requires C, 66·0; H, 8·9%). From mother-liquors, and by esterification of the mother-liquors of the monomethyl ester (XXVIII), a further 15 mg. were collected.

Methyl 7-*Acetoxyperhydro*-1-*hydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetate*-2-*carboxylate* α and β (XXVIII; R = Ac, R′ = Me).—A mixture of the above dimethyl ester (93·5 mg.), pyridine (0·4 c.c.), and acetic anhydride (0·2 c.c.) was kept for 24 hours and the neutral product then isolated. The *dimethyl acetoxy*-ester α (90 mg.) crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 117·5—118·5°, $[\alpha]_D^{23}$ −15° (*c* 1·6 in MeOH) (Found: C, 65·1; H, 8·8. $C_{23}H_{36}O_7$ requires C, 65·1; H, 8·5%). Hydrogenation of 2-carbomethoxy-$\Delta^{9(14)}$-dodecahydro-1 : 7-dihydroxy-2 : 13-dimethylphenanthrene-1-acetic acid β (110 mg.) afforded the monomethyl ester β (XXX; R = R′ = H) as diamond-shaped leaflets, m. p. 196°, from dilute acetic acid. Esterification with diazomethane gave the dimethyl ester (XXX; R = H, R′ = Me), leaflets (from ether), m. p. 141—142°, $[\alpha]_D^{22}$ −4° (*c* 1·2 in MeOH); and on acetylation *methyl* 7-*acetoxyperhydro*-1-*hydroxy*-2 : 13-*dimethylphenanthrene*-1-*acetate*-2-*carboxylate* β (XXX; R = Ac, R′ = Me) (75 mg.) was obtained. It crystallised from petrol in plates, m. p. 116—117°, strongly depressed by admixture with the α isomer, and had $[\alpha]_D^{23}$ −12° (*c* 1 in MeOH) (Found: C, 65·6; H, 8·1. $C_{23}H_{36}O_7$ requires C, 65·1; H, 8·5%).

Methyl 3(β)-*Benzoyloxyætio*allo*bilianate* (XXIX; R = Bz).—The dimethyl acetoxy-ester α (80 mg.) in pyridine (3 c.c.) was cooled in ice and treated with phosphoryl chloride (0·3 c.c.); the mixture was then refluxed for 1½ hours, and the product isolated as described above (B series). A gum (75 mg.) of $[\alpha]_D^{23}$ −12° (in Et_2O) was obtained. It was passed in pure ether through alumina (2 g.); the ether was replaced by acetic acid (3 c.c.), platinum oxide (34 mg.) added, and the mixture shaken with hydrogen for 20 hours. The specific rotation (in ether–acetic acid) was then about +3°. The product crystallised partly when seeded with methyl 3(β)-acetoxyætio*allo*bilianate (XXIX; R = Ac), and the crystals were lævorotatory; but this derivative did not seem satisfactory for purification. The total product was therefore dissolved in methanolic hydrogen chloride (2 c.c. of 1·5N); the solution was kept overnight, refluxed for 0·5 hour, and treated as usual for recovery of the neutral product. This was treated in a little pyridine with benzoyl chloride (0·1 c.c.). After 1 hour water was added and the neutral product isolated, dissolved in a few drops of light petroleum (b. p. 60—80°), and seeded with a trace of methyl 3(β)-benzoyloxyætio*allo*bilianate; crystallisation set in. Next day there were two kinds of crystals: fine, hairy needles and thick plates. On gentle warming, the needles dissolved; from the decanted solution a further crop of plates separated after 48 hours, and the needles

did not reappear. These two crops were recrystallised from light petroleum (b. p. 60—80°) and united; the whole (13 mg.) was recrystallised once more, the double melting point (in a capillary) remaining unchanged at 140° and 150—151°. The final yield of twice recrystallised material was 9 mg. The double melting points (in a capillary) were not depressed on mixing with the " natural " substance (XXII) (see p. 579). On the microscope hot-stage fine hair-like needles started growing from the elongated plates of the " synthetic " substance at 140°, and at 141·5° the unchanged plates melted, the needles finally melting at 154—155°. On admixture with the " natural " substance (which underwent these changes at 142°, 145°, and 158—159° respectively) the same phenomena occurred, the needles finally melting at 154—159°. The " synthetic " substance had $[\alpha]_D$ −16° and the " natural " $[\alpha]_D^{15}$ −16·2°. The rotations were also determined in a micro-tube by Dr. F. B. Strauss, who found : " synthetic " $[\alpha]_D^{20}$ −21·9° (*c* 2 in $CHCl_3$); natural $[\alpha]_D^{20}$ −18·3° (*c* 3 in $CHCl_3$). Analyses of the same quantities of both *esters* gave : " Synthetic " C, 72·0; H, 8·1. " Natural " C, 71·4; H, 7·5% ($C_{28}H_{38}O_6$ requires C, 71·5; H, 8·1%).

We are very grateful to Dr. Cowan for the following report.

" The ' natural ' and ' synthetic ' specimens examined were both nicely crystalline, growing as needles. The natural crystals were quite large, the ' synthetic ' consisting of rather small, slender needles. The crystals were monoclinic with *b* parallel to the needle axis. The (100) and (001) faces were almost equally developed in most crystals giving a roughly diamond-shaped cross section. Crystal shape and optics were similar for both specimens.

" *X*-Ray powder photographs of the ' natural ' and ' synthetic ' materials showed a majority of lines having spacing and relative intensity the same but each photograph appeared to have a few weak lines which did not correspond to any of those of the other. This observation could either be interpreted as due to slight, but significant, differences in crystal structure, or to traces of impurities in the crystals. It was therefore necessary to take single crystal photographs to check this result.

" *X*-Ray photographs taken for crystals of each specimen mounted about the [010] and [001] axes were found to be identical, thus confirming that the non-correspondence of certain lines in the powder photographs was due to traces of impurities, mainly in the synthetic specimen. The dimensions of the monoclinic unit cell are as follows : $a = 14{\cdot}07$, $b = 6{\cdot}04$, $c = 15{\cdot}05$ Å, $\beta = 94{\cdot}7°$. The space group is P_{2_1}. P. M. Cowan. D. M. Crowfoot Hodgkin. [Laboratory of Chemical Crystallography, University Museum, Oxford. May 1951.] "

When the dimethyl acetoxy-ester β (XXX; R = Ac, R′ = Me) (63 mg.) was submitted to the same process of dehydration, hydrogenation, alcoholysis, and benzoylation, the product crystallised partly. On recrystallisation from light petroleum (b. p. 60—80°), colourless plates, m. p. 155°, were obtained; on recrystallisation of these from methanol, pearly plates, m. p. 146°, resulted. This product on analysis was found to have retained the tertiary hydroxyl group, and was therefore *methyl 7-benzoyloxyperhydro-1-hydroxy-2 : 13-dimethylphenanthrene-1-acetate-2-carboxylate* β (Found : C, 69·0; H, 7·3. $C_{28}H_{38}O_7$ requires C, 69·1; H, 7·9%).

Carboxylation of 7-Benzoyloxyperhydro-1-keto-2 : 13-dimethylphenanthrene.—The *benzoyl* derivative, prepared in the usual manner from the hydroxy-ketone (Achtermann, *Z. physiol. Chem.*, 1934, **225**, 141; Billeter and Miescher, *Helv. Chim. Acta*, 1950, **33**, 388), crystallised from methanol in colourless prisms, m. p. 137—138°, $[\alpha]_D^{20}$ +10·7° ± 5° (*c* 0·4 in $CHCl_3$) (Found : C, 77·4; H, 8·2. $C_{23}H_{30}O_3$ requires C, 78·0; H, 8·5%).

This Achtermann ketone benzoate (820 mg.) in benzene (10 c.c.) was treated with a slight excess of ethereal sodium triphenylmethide. The suspension was then added to chopped solid carbon dioxide. When evolution of carbon dioxide had ceased the mixture was shaken with ice-water, and the resulting emulsion was broken in a refrigerated centrifuge. The aqueous extract was extracted with a further quantity of ether and was then acidified with ice-cold 2N-sulphuric acid. The liberated keto-acids were extracted with ether–benzene and esterified with ethereal diazomethane. The methyl esters, after removal of the ether, were chromatographed on alumina. Benzene–petrol (1 : 1) eluted methyl triphenylacetate, m. p. 182—183°. Benzene–chloroform (4 : 1) eluted two *keto-esters*, (i) colourless prisms (from methanol), m. p. 135—136°, $[\alpha]_D^{20}$ −55·6° ± 2° (*c* 0·7 in $CHCl_3$) (Found : C, 72·8; H, 8·0. $C_{25}H_{32}O_5$ requires C, 72·8; H, 7·8%), and (ii) elongated plates (from methanol), m. p. 164—165°, $[\alpha]_D^{20}$ −48·8° ± 3° (*c* 0·8 in $CHCl_3$) (Found : C, 72·5; H, 8·8%). The overall yield was low and an accurate estimate of the relative amounts of the isomeric esters could not be made, but they appeared to be present in comparable amount, the ester (ii) possibly being the more abundant.

Preparation of bilianic acid and syntheses of tetracylic ketones.

Reduction of Androst-4-ene-3 : 17-dione.—Androstenedione (5·0 g.) in ethanol (50 c.c.) was hydrogenated at room temperature and pressure in the presence of palladised strontium carbonate (850 mg.); one mol. of hydrogen was absorbed in 19 minutes. The product readily crystallised from *n*-hexane in elongated plates, m. p. 90—92°, not raised on repeated crystallisation. Occasionally it crystallised in prisms of two kinds that could be separated mechanically; both had m. p. 126—128°, but much lower on admixture. The entire product was then separated into these two substances by repeated chromatography on alumina. First androstane-3 : 17-dione, m. p. 128—129° (eluted with benzene–petrol, 1 : 9), and then testane-3 : 17-dione, m. p. 128—129° (eluted with benzene–petrol, 1 : 1), were obtained in approximately equal quantities. Paland, quoted by Butenandt, Tscherning, and Hanisch (*Ber.*, 1935, **68**, 2099), stated that reduction of androstenedione gave androstane-3 : 17-dione.

3β-*Hydroxyætiobilienic Acid* (X).—This acid was isolated in 0·9% overall yield from crude acids obtained as by-products of the oxidation of cholesteryl acetate dibromide *via* the water-soluble potassium salts. This material was kindly supplied by British Drug Houses Ltd. The dipotassium salt was precipitated from methanolic solution (cf. Kuwada, *J. Pharm. Soc. Japan*, 1936, **56**, 75; Wieland and Miescher, *Helv. Chim. Acta*, 1948, **31**, 211), and the recovered and purified acid had m. p. 240—241° (decomp.), alone or mixed with an authentic specimen kindly provided by Dr. E. B. Hershberg. The dimethyl ester, m. p. 112—112·5° (Kuwada, *loc. cit.*, gives m. p. 112°), had $[\alpha]_D^{20}$ −77° (*c* 5·2 in $CHCl_3$). Neither the acid nor the ester decolorised bromine in acetic acid at room temperature but did so rapidly at 50—60°.

3β-*Hydroxyætio*allo*bilianic Acid* (XXXI; R = R′ = H).—The bilienic acid (3·9 g.) in glacial acetic acid (60 c.c.) was hydrogenated in the presence of platinic oxide (200 mg.). After 4 hours the solution was filtered from the catalyst, and the solvent removed under reduced pressure. The bilianic acid crystallised from aqueous methanol in colourless needles, m. p. 238° (decomp.) (Kuwada and Miyasaka, *J. Pharm. Soc. Japan*, 1936, **65**, 631, give m. p. 239°), which did not decolorise bromine in acetic acid at 50—60°. The *dimethyl* ester, prepared by means of diazomethane, crystallised from benzene–light petroleum (b. p. 60—80°) in colourless prisms, m. p. 111—112°, $[\alpha]_D^{20}$ −23·7° (*c* 1·13 in $CHCl_3$) (Found: C, 68·6; H, 9·5. $C_{21}H_{34}O_5$ requires C, 68·8; H, 9·4%). This ester was also obtained by direct hydrogenation of the dimethyl bilienate. It was then less easy to purify, presumably owing to contamination by the isomeric bilianic ester (rings A–B *cis*). The *benzoate* (XXII) of the dimethyl ester crystallised from light petroleum (b. p. 60—80°) in colourless, elongated prisms, m. p. (capillary) 149—150° with softening at 140°. On a microscope hot-stage, long needles started to grow out of the prisms at 142°, at 145—146° those prisms which had not changed into needles melted, and the needles finally melted at 158—159°. Very slow heating was essential for observation of this highly characteristic phenomenon. The derivative had $[\alpha]_D^{15}$ −16·2° (*c* 5·3 in $CHCl_3$), hence $[M]_D$ 3-benzoate *minus* 3-hydroxy, +15° (Barton, *J.*, 1945, 813, gives +2° ± 3° for this change in stanols) (Found: C, 71·4; H, 8·4. $C_{28}H_{38}O_6$ requires C, 71·5; H, 8·1%).

3β-*Hydroxyætio*allo*bilianic Acid* 17-*Methyl Ester* (XXXI; R = H, R′ = Me).—The dimethyl 3-hydroxy-ester (1·6 g.), potassium carbonate (0·5 g.), water (2 c.c.), and methanol (18 c.c.) were heated on a steam-bath for 24 hours with occasional addition of water (total 25 c.c.). The hot solution was acidified with 2N-hydrochloric acid. The crystalline *half-ester* (yield 95%) was recrystallised from aqueous methanol, forming colourless needles, m. p. 175—177° after being dried at 80° in a high vacuum, $[\alpha]_D^{17}$ −19·0° (*c* in MeOH) (Found: C, 68·1; H, 8·9. $C_{20}H_{32}O_5$ requires C, 68·2; H, 9·1%). The dimethyl benzoyloxy-ester was hydrolysed in a similar manner and the resulting 3-hydroxy-half-ester, after removal of benzoic acid by sublimation, had m. p. 176—177°, $[\alpha]_D^{17}$ −19·0°, alone or mixed with the above half-ester.

3β-*Acetoxyætio*allo*bilianic Acid* 17-*Methyl Ester* (XXXI; R = Ac, R′ = Me).—The above half-ester was acetylated (acetic anhydride–pyridine), and the product refluxed with aqueous acetic acid to hydrolyse any mixed anhydrides. The *acetoxy-half-ester* (yield, 80%) crystallised from aqueous acetone in colourless needles, m. p. 92—97°, $[\alpha]_D^{15}$ −28·1 (*c* 1 in EtOH), whence $[M]_D$ 3-acetate *minus* 3-hydroxy = −34° (Barton gives −34° ± 11° for stanols) (Found: C, 64·6; H, 8·8. $C_{22}H_{34}O_6,H_2O$ requires C, 64·1; H, 8·7%).

3β-*Acetoxyandrostan*-17-*one* (epi*Androsterone Acetate*) (XXXIII; R = Ac).—The acetoxy-half-ester (4·3 g.) was warmed with dry benzene (20 c.c.) and oxalyl chloride (10 c.c.) until evolution of hydrogen chloride ceased. The mixture was evaporated to dryness under reduced pressure on the steam-bath, and this process was thrice repeated with fresh quantities of dry benzene. The residual oil was dissolved in light petroleum (b. p. 60—80°) and filtered from some unchanged acetoxy-half-ester into an ice-cold ethereal solution of diazomethane (1 g.).

The mixture was kept overnight at −5° and the solvent then removed under diminished pressure at room temperature. The oily diazo-ketone did not crystallise and was treated in 95% ethanol at 50° with silver nitrate (2 g.) in aqueous ammonia (20 c.c.; *d* 0·880). After 2½ hours' refluxing the solution was concentrated *in vacuo* and extracted with ether. The oily amide, obtained on evaporation of the solvent, was dissolved in methanol (40 c.c.) containing potassium hydroxide (4 g.). The mixture was refluxed for 16 hours and then concentrated *in vacuo*. On acidification an oil separated from which a few crystals separated slowly. These were recrystallised several times from aqueous methanol and found to be the parent acid, m. p. 236—238° (Found : C, 67·2; H, 8·9. Calc. for $C_{19}H_{30}O_5$: C 67·5; H, 8·9%). The remaining oily acid (XXXII) was refluxed in acetic acid (200 c.c.) containing acetic anhydride (13 c.c.) for 6 hours. The solvent was removed by distillation, and the residue was heated to 250—260°/15 mm. for 15 minutes and then distilled at 0·001 mm. The clear distillate slowly crystallised, and was purified by chromatography. *epi*Androsterone acetate (overall yield 15%) crystallised from petrol in thick, colourless prisms, m. p. 103—104°, $[\alpha]_D^{18}$ +64·6° ± 2° (*c* 1 in $CHCl_3$), whence $[M]_D$ 3-acetate *minus* 3-hydroxy = −30° (Barton gives −34° ± 11° for stanols) (Found : C, 75·3, 75·6, 76·5; H, 9·4, 10·5, 9·5. Calc. for $C_{21}H_{32}O_3$: C, 75·9; H, 9·6%). Its m. p. was not depressed on admixture with a sample (prepared by the hydrogenation and re-oxidation of dehydro*epi*androsterone acetate), m. p. 101·5—103·4°, $[\alpha]_D^{18}$ +68·5° ± 2° (Found : C, 76·2; H, 9·6%). Barton (*J.*, 1946, 1116) gives $[\alpha]_D$ +69°. Ruzicka, Goldberg, and Brüngger (*Helv. Chim. Acta*, 1934, **17**, 1389, 1395) give m. p. 96—97° (but not a rotation) for a sample prepared by chromic acid oxidation of cholestanyl acetate; Butler and Marrian (*J. Biol. Chem.*, 1938, **124**, 237) give m. p. 115—118° for an acetate prepared from *epi*androsterone which had been isolated from the urine of a patient suffering from an adrenal tumour, but they give neither an analysis nor the optical rotatory power of the specimen. Drs. Hodgkin and Cowan reported that the two specimens were crystallographically identical.

Hydrolysis of the above synthetic acetate gave *epi*androsterone, m. p. 171—172° (Ruzicka *et al.*, *loc. cit.*, give m. p. 174—174·5°), alone or mixed with a specimen prepared by hydrolysis of the acetate obtained by degradation of tetracyclic material (see above).

Preparation of Dehydroepiandrosterone Acetate from Ætiobilienic Acid.—Our results agreed with one exception, with those given by Kuwada and Nakamura (*loc. cit.*), by Hershberg, Schwenk, and Stahl (*loc. cit.*), and by Heer and Miescher (*Helv. Chim. Acta*, 1947, **30**, 786). These authors state respectively that 3-acetoxyætiobilienic acid 17-methyl ester melted at 168·5—169·5°, 170—171·5°, and 167°. Our specimen crystallised from aqueous acetone in colourless, rectangular plates which, after being dried at 100° *in vacuo* for 2 hours, melted (capillary or micro-hot-stage) at 156—157°, then resolidified, and finally melted at 167° (Found : C, 67·8; H, 8·2. Calc. for $C_{22}H_{32}O_6$: C, 67·3; H, 8·2%).

Reduction of Androst-4-ene-3 : 17-dione Enol Acetate.—A mixture of androstenedione (11·0 g.), acetyl chloride (80 c.c.), and acetic anhydride (80 c.c.) was refluxed for 3 hours and then concentrated to about 20 c.c. under reduced pressure. On cooling, the enol acetate (10 g.) solidified. It crystallised from methanol in needles, m. p. 124—125° (Ruzicka and Fischer, *Helv. Chim. Acta*, 1936, **19**, 1371, give m. p. 127—129°).

This (10·0 g.) in ether (200 c.c.) was added, with stirring, to a solution of potassamide (from 10·0 g. of potassium) in liquid ammonia (750 c.c.), and the solution kept for an hour. Ammonium chloride (20 g.) was added, the solution set aside for a further hour, and the ammonia evaporated off. The residue was extracted with ether (5 × 200 c.c.), and the ethereal extract added immediately to a solution of lithium aluminium hydride (5·0 g.) in ether (500 c.c.). After 5 hours, more lithium aluminium hydride (2·0 g.) was added, and at the end of an hour the excess of lithium aluminium hydride and the complex were decomposed by the addition of ice-cold 10% hydrochloric acid, the solution also being cooled in ice. The ethereal layer was separated, the aqueous layer was extracted with ether, and the ethereal fractions were combined, washed with dilute sodium carbonate solution and with water, and dried. Removal of the solvent afforded first a yellow solid, m. p. 120—128°, $[\alpha]_D^{20}$ −20° in EtOH, and then a glass (total yield, 9 g.). The product was treated with ether–benzene (500 c.c.; 1 : 4) and purified by chromatography on alumina (150 g.) prepared in the same solvent (giving fraction A). A portion (1·7 g.; m. p. 115—120°, $[\alpha]_D^{23}$ −23° in EtOH) did not dissolve and was treated separately (fraction B).

The fraction (A), eluted by benzene–ether (4 : 1 and 7 : 3), was a solid (750 mg.), m. p. 100—105°, $[\alpha]_D^{18}$ +85° in EtOH. It was chromatographed in benzene (75 c.c.) on alumina (22·5 g.) prepared in benzene. The fraction eluted by benzene–ether (4 : 1) yielded a white solid crystallising from the solvent in needles (50 mg.), m. p. 150—154°, $[\alpha]_D^{19}$ +171° in EtOH. It could not be purified further, but appeared to be mainly androst-4-enedione (m. p. 174°, $[\alpha]_D$ +190°).

The portion eluted by benzene–ether (7 : 3) gave a solid crystallising from ether in needles (300 mg.), m. p. 105—108°, $[\alpha]_D^{21}$ +85° in EtOH. Further chromatographic purification yielded testosterone, m. p. 150°, $[\alpha]_D^{20\cdot5}$ +113° (*c* 2·5 in EtOH), ultra-violet absorption max. at 242·5 mμ (log ε 4·2) (Found: C, 78·4; H, 9·7. Calc. for $C_{19}H_{28}O_2$: C, 79·1, H, 9·7%). The physical constants for testosterone are m. p. 155°, $[\alpha]_D$ +109°, $\lambda_{max.}$ 238 mμ (log ε 4·1) (Ruzicka, *Helv. Chim. Acta*, 1935, **18**, 1264).

Further fractions were eluted by benzene–ether (3 : 2 and 1 : 1) and these afforded a white crystalline solid (1·42 g.; m. p. 123—128°, $[\alpha]_D^{21}$ −34° in EtOH). The solid was dissolved in benzene–ether (600 c.c.; 7 : 3) and chromatographed on alumina (45 g.) prepared in the same, solvent. The fractions eluted by benzene–ether (300 c.c.; 3 : 2) yielded a white solid crystallising from ether in needles, m. p. 158—162°, $[\alpha]_D^{20}$ −36° in EtOH. This was recognised as impure androst-5-enediol.

The solid B (1·7 g.; see above) was triturated with benzene–ether (600 c.c.; 7 : 3). A portion C (250 mg.) did not dissolve. The solution was chromatographed on alumina (45 g.) and a portion eluted by benzene–ether (300 c.c.; 3 : 2) yielded a white solid crystallising from ether in needles, m. p. 167—169°, $[\alpha]_D^{20}$ −44° in EtOH (750 mg.), but this material was not further examined.

The sparingly soluble residue C crystallised from ether in needles, m. p. 174°, $[\alpha]_D^{20}$ −46° in EtOH (Found: C, 74·2; H, 10·1. Calc. for $C_{19}H_{30}O_2,H_2O$: C, 74·0; H, 10·4%). The m. p was undepressed on admixture with androst-5-ene-3β : 17β-diol prepared by the reduction of dehydro*epi*androsterone, as follows.

A solution of dehydro*epi*androsterone (5·0 g.) in dry ether (200 c.c.) was added slowly, with stirring, to one of lithium aluminium hydride (2·0 g.) in ether (200 c.c.). After 16 hours the excess of lithium aluminium hydride and the complex were decomposed by the addition of ice-cold 10% hydrochloric acid. The product partly separated from the solution and was collected (3·5 g.; m. p. 175—176°). The ethereal layer and subsequent ethereal extracts were combined, washed with dilute potassium carbonate solution and with water, and dried. Removal of the solvent yielded the diol (XXXV; R = H) (400 mg.) which crystallised from ether in needles, m. p. 178°, $[\alpha]_D^{20}$ −50° in EtOH (Found: C, 74·3; H, 10·3. Calc. for $C_{19}H_{30}O_2,H_2O$: C, 74·0; H, 10·4%).

3-*Triphenylmethoxyandrost-5-en*-17-*one*.—A solution of dehydro*epi*androsterone (1·0 g.) and triphenylmethyl chloride (900 mg.) in pyridine (2 c.c.) was heated on the steam-bath for 4 hours and then added to water. The product was isolated by means of ether and freed from pyridine. The oil (1·9 g.) was dissolved in benzene–petrol (200 c.c.; 1 : 9) and purified by chromatography on alumina (60 g.), prepared in petrol. The fraction eluted by benzene–petrol (2 : 3) yielded the required *ether* (657 mg.) as clusters of fine needles (from petrol), m. p. 198°, $[\alpha]_D^{19}$ −7° (*c* 1·08 in $CHCl_3$) (Found: C, 85·8; H, 7·6. $C_{38}H_{42}O_2$ requires C, 86·0; H, 7·9%).

3-*Triphenylmethoxyandrost-5-en*-17-*ol* (XXXV; R = CPh_3).—(*a*) The foregoing ketone ether (444 mg.) in ether (30 c.c.) was added to a solution of lithium aluminium hydride (200 mg.) in ether (30 c.c.) and kept for 20 hours. The excess of lithium aluminium hydride was decomposed by the addition of ice, and the complex by ice-cold 10% hydrochloric acid. The ethereal layer (A) was separated, the aqueous layer shaken with ether (B), and the extracts A and B were combined, washed with dilute potassium carbonate solution and with water, and dried. On removal of the solvent the *product* crystallised (335 mg.) in needles, m. p. 210°, $[\alpha]_D^{19}$ −43° (*c* 1·04 in $CHCl_3$) (Found: C, 84·2; H, 8·2. $C_{38}H_{44}O_2,0{\cdot}5H_2O$ requires C, 84·3; H, 8·3%). On admixture with the starting material the m. p. was depressed to 175—192°.

(*b*) Androst-5-ene-3 : 17-diol (4·1 g.) and triphenylmethyl chloride (4·0 g.) in pyridine (8 c.c.) were heated on the steam-bath for 6 hours. The product was isolated by means of ether (2·0 g. of solid separated). On removal of the dried solvent, the product crystallised in the successive fractions: (1) 680 mg., m. p. 135—150°; (2) 150 mg., m. p. 155—176°; (3) 560 mg., m. p. 150—153°; (4) 700 mg., m. p. 149—151°; and (5) 1·44 g., m. p. 145—150°. The first three fractions were unchanged androstenediol. Fractions (4) and (5) were combined and chromatographed in benzene–petrol (200 c.c.; 1 : 4) on alumina (60 g.) prepared in petrol. The fractions eluted by benzene–petrol (2 : 3), changing to pure benzene, yielded triphenylmethanol (800 mg.), and those by benzene–ether (2 : 3) yielded 3-triphenylmethoxyandrost-5-en-17-ol (121 mg.), m. p. 211°, $[\alpha]_D^{20}$ −42° (*c* 1·14 in $CHCl_3$), the m. p. being undepressed by admixture with an authentic specimen of this compound, prepared as described above (Found: C, 84·4; H, 8·2%). By recrystallisation in a dry atmosphere from carefully dried ether the anhydrous *compound*, m. p. 211°, was obtained (Found: C, 85·2; H, 8·4. $C_{38}H_{44}O_2$ requires C, 85·5; H, 8·3%).

Oxidation of 3-*Triphenylmethoxyandrost-5-en*-17-*ol*.—To a boiling mixture of the foregoing

alcohol (373 mg.), *cyclo*hexanone (3 c.c.), and toluene (16 c.c.), aluminium *iso*propoxide (300 mg.) in toluene (6 c.c.) was added. The solution was refluxed for 3 hours, and then distilled in steam. The residue was made acid with dilute hydrochloric acid, and extracted with ether with the usual technique. The oily product was chromatographed in benzene–petrol (30 c.c.; 1 : 4) on alumina (9 g.) prepared in petrol. The fractions eluted by benzene–petrol (2 : 3) yielded the ketone as clusters of white needles (180 mg.), m. p. 198°, $[\alpha]_D^{21}$ −6° (*c* 1·14 in $CHCl_3$), from petrol (Found : C, 86·0; H, 7·8. Calc. for $C_{38}H_{42}O$: C, 86·0, H, 7·9%). The m. p. was undepressed on admixture with an authentic specimen.

Hydrolysis.—The triphenylmethoxy-ketone (200 mg.) in dry chloroform (10 c.c.) was mixed with chloroform (25 c.c.) saturated with hydrogen chloride, the solution being cooled in ice. Hydrogen chloride was passed in for 15 minutes, and after 0·5 hour at the room temperature the chloroform solution was washed with dilute potassium carbonate solution and with water, and dried. The solvent was removed, and the product (200 mg.) chromatographed in benzene–petrol (20 c.c.; 1 : 4) on alumina (6 g.) prepared in petrol. The fractions eluted by benzene–petrol (2 : 3) yielded unchanged starting material (11 mg.), and those by benzene–petrol (1 : 1) and by benzene gave triphenylmethanol (45 mg.), m. p. 158° undepressed on admixture with a genuine specimen. The fraction eluted by benzene–ether (1 : 1) yielded dehydro*epi*androsterone (59 mg.), m. p. 147°, undepressed on admixture with an authentic specimen.

Androst-4-ene-3α : 17β-diol and -3β : 17β-diol.—Lithium aluminium hydride (35 mg.) in ether (20 c.c.) was added to androst-4-ene-3 : 17-dione (700 mg.) in ether (100 c.c.) during 10 minutes. After a further 15 minutes the complex was decomposed by dilute hydrochloric acid, the ethereal layer separated, the aqueous layer extracted with ether, and the ethereal extracts were combined, washed with sodium hydrogen carbonate solution and with water, and dried. Removal of the solvent left a solid (0·7 g.) which was chromatographed in benzene–petrol (100 c.c., 1 : 1) on alumina (30 g.) prepared in the same solvent. The fraction eluted by benzene–ether (400 c.c., 9 : 1) was unchanged androst-4-ene-3 : 17-dione (206 mg.), m. p. 168°, $[\alpha]_D$ +198° (*c* 1·0 in $CHCl_3$); that eluted by benzene–ether (400 c.c.; 1 : 1) gave androst-4-ene-3α : 17β-diol, crystallising from ether in needles (170 mg.), m. p. 149—150°, $[\alpha]_D$ +78° (*c* 0·98 in $CHCl_3$) (Found : C, 76·4; H, 10·3. Calc. for $C_{19}H_{30}O_2,0{\cdot}5H_2O$: C, 76·2; H, 10·4%).

The fractions eluted by benzene–ether (300 c.c., 2 : 1) and ether (100 c.c.) yielded androst-4-ene-3β : 17β-diol, crystallising from ether in needles (100 mg.), m. p. 212—215°, $[\alpha]_D^{19}$ +102° (*c* 2·22 in EtOH) (Found : C, 79·2; H, 10·0. Calc. for $C_{19}H_{30}O_2$: C, 78·7; H, 10·3%). Butenandt and Heuser (*Ber.*, 1938, **71**, 198) give m. p. 154°, $[\alpha]_D^{19}$ +48·5° (in EtOH) for androst-4-ene-3α : 17β-diol, and m. p. 202—206°, $[\alpha]_D^{22}$ +187·5° (in pyridine) for androst-4-ene-3β : 17β-diol.

iso*Hexylation of Pregnenolone Acetate.*—The reaction of *iso*hexylmagnesium bromide with 3-acetoxypregn-5-en-20-one was carried out in the usual manner and the isolated product was re-acetylated. Chromatography on alumina afforded a product, m. p. 98—100°, $[\alpha]_D^{14}$ −13° in $CHCl_3$ (Found : C, 79·1, 79·8; H, 9·6, 9·4%). This was probably a mixture (or compound) of pregna-3 : 5-diene-20-one (Calc. : $[\alpha]_D$ −69°; C, 84·6; H, 10·1%) and 20-hydroxycholesteryl 3-acetate or its 17 : 20-stereoisomeride (Calc. : $[\alpha]_D$ *ca.* −38°; C, 78·4; H, 10·8%).

After dehydration with toluene-*p*-sulphonyl chloride and pyridine, and isolation (chromatography), a product, m. p. 108°, $[\alpha]_D$ −21°, $\lambda_{max.}$ 236 and 265 (log ε 4·1 and 2·9 respectively) (Found : C, 83·5, 82·3; H, 10·1, 9·9%), was obtained. This may be a mixture of pregnadienone [$\lambda_{max.}$ 235 (log ε 4·2)] with 17 : 20-dehydrocholesteryl acetate (Calc. : $[\alpha]_D$ −38°; C, 81·7; H, 10·8%). Hydrogenation over palladium afforded material, m. p. 87°, $[\alpha]_D$ +98° (Found : C, 83·5; H, 10·8%), and then over platinic oxide material, m. p. 109—111°, $[\alpha]_D$ +77·5° (Found : C, 81·8, 84·2; H, 10·4, 11·2%). This showed a carbonyl band in the infra-red spectrum and was doubtless impure *allo*pregnan-20-one (Shoppee, Lewis, and Elbs, *Chem. and Ind.*, 1950, 454, give m. p. 129°, $[\alpha]_D$ +99°. Calc. : C, 83·4; H, 11·2%). Our impression was that the initial Grignard reaction had not worked well and that such *iso*hexylated product as was produced gradually disappeared in the extensive adsorption processes used for purification at all stages.

Dihydropyran Adduct of Pregnenolone (XXXVII).—Pregnenolone (1·0 g.) was dissolved in dihydropyran (15 c.c.) and two drops of concentrated hydrochloric acid were added. The solution was warmed on the steam-bath for 1½ hours, cooled, and made alkaline with methanolic potassium hydroxide. The oily product was isolated with the aid of ether and solidified when rubbed with petrol. The *derivative* crystallised from methanol in white, glistening plates (870 mg.), m. p. 124—125°, $[\alpha]_D^{19}$ +18° (*c* 1·18 in $CHCl_3$) (Found : C, 77·9; H, 10·1. $C_{26}H_{40}O_3$ requires C, 78·0; H, 10·0%). Reaction of this substance with *iso*hexylmagnesium bromide and chromatography of the product gave material, m. p. 95—98°, $[\alpha]_D^{15}$ +11° (Found : C, 77·9; H, 10·2%); acetylation and dehydration by phosphoryl chloride and pyridine g ound,

m. p. 117°, $[\alpha]_D$ +40°, and, after hydrogenation over platinic oxide, *allo*pregnan-20-one, m. p. 127°, $[\alpha]_D$ +81° (carbonyl band in the infra-red spectrum), was the only product isolated by chromatography.

Preparation of iso*Hexyl Bromide* (*1-Bromo-4-methylpentane*).—A solution of *iso*amyl bromide (112 g.; reputedly pure commercial specimen, refractionated) in ether (500 c.c.) was added to magnesium (17·6 g.) at such a rate that the ether refluxed gently. The solution was warmed for a further 30 minutes, cooled in ice–salt, and powdered solid carbon dioxide was gradually added so that the temperature did not rise above 0° (3 hours). The mixture was stirred for 2 hours at the room temperature, cooled, and decomposed with 20% hydrochloric acid (250 c.c.). The acidic product (53 g.), distilled through an efficient fractionating column, had b. p. 118—120°/20 mm. (yield, 35 g.).

The *iso*hexanoic acid (35 g.) in ether (500 c.c.) was added to a slurry of lithium aluminium hydride (12·0 g.) in ether (400 c.c.), cooled in methanol and solid carbon dioxide. When the addition was complete (1 hour) the mixture was stirred for 2 hours at the room temperature, then cooled and worked up in the known manner. The yield of *iso*hexanol, b. p. 148—150°, was 21 g. The bromide, prepared by Sabetay and Bléger's method (*Bull. Soc. chim.*, 1930, **47**, 885), had b. p. 144° (Found: C, 43·4; H, 7·8; Br, 48·5. Calc. for $C_6H_{13}Br$: C, 43·6; H, 7·9; Br, 48·5%).

3β-*Acetoxycholest*-17(20)-*ene* (XXXVIII).—3β-Acetoxy*allo*pregnan-20-one (2·6 g.) in anisole (25 c.c.) was added with vigorous stirring to a solution of *iso*hexylmagnesium bromide (from 1·0 g. of *iso*hexyl bromide and 1·02 g. of magnesium) in anisole (50 c.c.), and the solution refluxed for 3 hours. After the addition of 50% hydrochloric acid (5 c.c.), the anisole was removed by steam-distillation. The product was isolated by means of ether, and the extract washed with sodium hydrogen carbonate solution, then with water, and dried (Na_2SO_4). Removal of the solvent yielded a viscous oil (3·0 g.; probably cholestane-3 : 20-diol) which was refluxed for 2½ hours with glacial acetic acid (25 cc.). The solvent was removed under reduced pressure, acetic anhydride (25 c.c.) added, and the solution again refluxed for ½ hour. The acetic anhydride was removed under reduced pressure, the product dissolved in ether, and the ethereal solution washed with sodium hydrogen carbonate solution and with water, and dried. Removal of the solvent left an oil (3 g.) which was chromatographed in petrol (100 c.c.) on alumina (30 g.). The fractions eluted by petrol (200 c.c.) and by petrol–benzene (400 c.c.; 9 : 1) yielded an oil which was chromatographed again in petrol (100 c.c.) on alumina (90 g.). Elution by 100-c.c. portions of petrol yielded ten fractions which could not be crystallised; ten 100-c.c. portions of benzene–petrol (1 : 9) eluates behaved similarly. The combined oils (A) (1·75 g.) had $[\alpha]_D$ +10° (*c* 0·72 in $CHCl_3$). The column was washed with petrol–ether (100 c.c.; 1 : 1), and ether, and yielded semicrystalline pastes (0·35 g. and 0·18 g.) which were combined and chromatographed in petrol (60 c.c.) on alumina (15 g.). Elution by 60-c.c. portions of petrol yielded as the third fraction, a waxy solid (0·5 g.), which was triturated repeatedly with methanol, finally being cooled in solid carbon dioxide–methanol, powdered, and allowed to warm to the room temperature; the solvent was replaced, and the process repeated. 3β-Acetoxycholest-17(20)-ene was obtained as a white waxy solid (B) (0·23 g.), m. p. 65—74°, which crystallised from methanol in needles, m. p. 86—88°, $[\alpha]_D$ +2° (*c* 0·92 in $CHCl_3$) (Found: C, 81·1; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·3; H, 11·2%).

Reduction of 3β-*Acetoxycholest*-17(20)-*ene*.—(*a*) The oil (A) (1·75 g.) from the previous experiment was hydrogenated in acetic acid (100 c.c.) with a trace of perchloric acid over Adams's platinum oxide. The solution was then poured into water (150 c.c.) and extracted with chloroform. The chloroform extract was washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Removal of the solvent yielded an oil (1·3 g.) which was chromatographed in petrol (100 c.c.) on alumina (60 g.), prepared in petrol. Elution by 100-c.c. portions of petrol yielded three oily fractions. Elution with ether–petrol (1 : 19) yielded only traces of oil, but on washing of the column with ether (100 c.c.) a waxy solid (150 mg.) was obtained, which crystallised from methanol in glistening needles, m. p. 109—110°, $[\alpha]_D^{17}$ +12·8° (*c* 0·94 in $CHCl_3$) (Found: C, 81·4, 80·6; H, 11·6, 11·5. Calc. for $C_{29}H_{50}O_2$: C, 80·9; H, 11·6%). The m. p. was undepressed on admixture with an authentic specimen of cholestanyl acetate, m. p. 110—111°, $[\alpha]_D^{16}$ +13°, obtained by the reduction of chlolesterol (Nace, *J. Amer. Chem. Soc.*, 1951, **73**, 2379) followed by acetylation. The infra-red spectra of the natural and synthetic specimens were identical. The following is a report on the *X*-ray diffraction properties.

"*Cholestanyl acetate*. Single crystals from the natural and synthetic samples have been examined, and found to be identical.

"The unit cell is monoclinic, with the approximate dimensions a = 10·2 Å, b = 39·6 Å, c = 7·6 Å, β = 103°. March, 1952. Mrs. D. M. Crowfoot Hodgkin and Dr. B. M. Oughton."

The oil from which the cholestanyl acetate had been removed was hydrolysed by boiling 10% methanolic potassium hydroxide (100 c.c.). Water (150 c.c.) was added, and the solution worked up as usual to yield an oil (0·61 g.) which gave no precipitate with digitonin in alcohol. The infra-red absorption spectrum of this oil showed that it contained ketonic material.

(*b*) 3β-Acetoxycholest-17(20)-ene (B) (168 mg.) in acetic acid (20 c.c.) containing a trace of perchloric acid was hydrogenated during 15 minutes over Adams's catalyst. The product, isolated as usual, crystallised from methanol in needles, m. p. 108° $[\alpha]_D^{17}$ +14·3° (*c* 0·7 in $CHCl_3$) (Found : C, 81·1 ; H, 11·3. Calc. for $C_{29}H_{50}O_2$: C, 80·9, H, 11·6%). The m. p. was undepressed on admixture with an authentic specimen of cholestanyl acetate, and the infra-red spectra of the two materials were identical.

From the mother-liquors two further crops, m. p. 72—74°, $[\alpha]_D$ +16·5°, and m. p. 55—60°, were obtained. They could not be purified by crystallisation, and were combined and hydrolysed by boiling 10% methanolic potassium hydroxide (25 c.c.) for an hour. On dilution with water the product was precipitated ; it crystallised from methanol in needles, m. p. 106—110°, $[\alpha]_D^{16}$ +17·3° (*c* 0·99 in $CHCl_3$), which gave no digitonide in methanol.

At this culmination of an investigation commenced in 1932, it is appropriate to express gratitude to the Rockefeller Foundation of New York, both for the provision of funds that made possible the building of the extension of this laboratory in which much of the work was prosecuted, and also for grants and gifts over a long period. We are also grateful to Imperial Chemical Industries Limited for a considerable grant for equipment, as well as for recurrent grants and gifts of material.

We are deeply indebted to British Drug Houses Ltd. for generous gifts of valuable residues and of a large specimen of androstenedione. We thank Dr. E. B. Hershberg and the Schering Corporation of America Inc. for various specimens and for residues from cholesteryl acetate dibromide oxidations. We thank Messrs. CIBA Limited for a generous gift of the pure Köster–Logemann keto-acetate. Grateful acknowledgment is made of the support given by Nyegaard and Co A/S, Oslo, and by the Royal Norwegian Council for Scientific Research to one of us (H. H.). This work was carried out during the tenure of an I.C.I. Fellowship (H. M. E. C.) and of an 1851 Overseas (Eire) Scholarship (S. R. D.).

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77. *The Electrolytic Production of Quadrivalent Uranium.*

By H. K. El-Shamy and S. El-Din Zayan.

The conditions for the complete electrolytic reduction of acid uranyl chloride solutions to quadrivalent uranium have been studied, especially the factors affecting the limiting current density and hence the efficiency of the main cathodic process. The reduction was followed quantitatively through time–potential curves under various conditions.

Apart from the polarograms obtained by Harris and Kolthoff (*J. Amer. Chem. Soc.*, 1945, **67**, 1884 ; 1946, **68**, 1175 ; 1947, **69**, 446) little work has been reported on the electrolytic reduction of uranyl solutions to quadrivalent uranium, and most of it was directed to the determination of uranium as electrolytically deposited hydrated yellow or black oxides ; the electro-reduction of uranyl salts at a mercury cathode was also made the basis of a process for the determination of uranium (Sutton, *J. Nat. Res. Council*, Canadian Atomic Energy Project, N.R.C. No. 1591, 1945). For these reasons and also because of the possible use of quadrivalent uranium for determining the standard redox potential of the uranium system, interest has been focused particularly on the production of uranous solutions in a high state of purity.

The work now reported clarifies the optimum conditions for the complete electrolytic reduction of uranyl chloride to the quadrivalent state in solutions containing hydrochloric acid. Different experimental conditions were tried in order to study the cathodic process and particularly the factors affecting the limiting current density and hence the efficiency

of the main reduction process : these factors were the concentration of uranyl ions, acidity of solutions, temperature, rate of stirring of catholyte, and nature of electrode.

Experimental

Materials.—The reagents used were of high grade (B.D.H.), and the uranyl solutions were analysed for uranium gravimetrically as U_3O_8. The bright electrode was a cylindrical platinum wire gauze of 12·56 cm. circumference and 4 cm. high. A similar electrode was coated with spongy platinum-black, and a third was gold-plated. Each experiment was carried out with a freshly prepared electrode, washed thoroughly with distilled water and then with the solution to be used for electrolysis.

Electrolytic Reduction Cell.—The reaction vessel was a 400-ml. Pyrex beaker fitted with a rubber stopper provided with six openings for the following parts : (1) The stirrer, which consisted mainly of the two glass parts of a syringe, was moved by a D.C. motor that allowed regular and easily controlled stirring. (2) The anode element, which was enclosed in a thin porous clay compartment, consisted of a platinum wire 20 cm. long sealed into a glass tube fitted with an outer jacket and a gas inlet and exit for carbon dioxide; this served, when necessary, to sweep any accumulated chlorine away from the anode compartment and prevent possible diffusion to the catholyte. (3) The cathode element. (4) The salt-bridge was provided with a reservoir at the upper end of the limb dipping into the catholyte to eliminate gas bubbles when experiments were carried out at high temperatures; it was refilled before each experiment to minimise diffusion of foreign ions into the potassium chloride solution. (5) The indicator electrode was made of a platinised platinum sheet 1 × 2 cm. (6) The gas inlet and exit for carbon dioxide were fitted with mercury traps. These different parts were inserted through ground joints to allow their removal when required. A layer of mercury was spread over the rubber stopper to prevent ingress of atmospheric oxygen. The cell was then kept in an adjustable constant-temperature bath. The carbon dioxide used was purified by passage through leuco-indigo-carmine and chromous sulphate solutions.

Determination of the Cathode Potential.—Direct measurements of the different potentials maintained at the cathode under examination while current strength was varied were made by connecting the cathode through a salt-bridge, to a saturated calomel reference electrode and measuring the e.m.f. thus formed by means of a sensitive potentiometer, sufficient time being allowed for constant conditions to be attained. The error due to any ohmic fall of potential across the solution was minimised by drawing out the end of the salt-bridge to a moderate capillary and placing it close to the surface of the cathode. Before an electrolysis was started, purified carbon dioxide gas was bubbled through the solution.

Results.—Effect of concentration of uranyl ions. Solutions were 1·4M in hydrochloric acid and 0·0461, 0·0692, or 0·0922M in uranyl chloride. The limiting current density was found to vary almost in proportion to the concentration of uranyl ions. The effective thickness of the diffusion layer remained, however, constant in all cases. These investigations were made at room temperature without stirring of the catholyte, but results on stirred solutions were similar.

Effect of acidity. Solutions were stirred at 550 r.p.m. and were 0·0461M with respect to uranyl-ion concentration. Experiments were carried out both at room temperature and at 80° while the concentration of the free hydrochloric acid was varied between 0·1 and 7·5M. The limiting current density was found to increase with acid concentration up to 6M and then decreased at higher acidities owing probably to some sort of concentration polarisation and the deposition of thin grey films on the cathode.

Effect of temperature. Solutions were equally stirred and the acidity was kept at 2M and the uranyl concentration at 0·0461M while the temperature was altered from 30° to 80°. The limiting current density was found to increase with rise of temperature, the value at 80° being about 1·5 times that at 30°.

Effect of stirring. Solutions were 0·0922M with respect to uranyl-ion concentration and 1·4M in hydrochloric acid. The rate of stirring of the catholyte varied between 350 and 1600 r.p.m. The limiting current density was found to rise with increase in rate of stirring, and the thickness of the diffusion layer decreased but was never eliminated. It was also found that stirring had a greater effect on the limiting current density than rise of temperature.

Type of electrode. The limiting current density was comparatively high with platinised platinum and low with bright electrodes. The bubble hydrogen over-voltage potential, beyond which hydrogen was freely evolved, was lowest with platinised electrodes. Since high over-voltage cathodes allow the possibility of greater degree of reduction, lead and mercury cathodes

were tried. The former were unsuitable, as they reacted with the acid present, turning uranyl solutions green before the current was applied. The mercury cathodes gave better results, and the values obtained for the limiting current density were the lowest of those for inert electrodes, the bubble hydrogen over-voltage being comparatively high. In all cases, the results indicated only one stage in the reduction to quadrivalent uranium.

In the reduction process, acid uranyl chloride solutions were used as catholytes, and hydrochloric acid solutions of the same concentration as anolytes. The reduction was followed quantitatively, under various conditions, through time–potential curves. The prevailing redox potentials during reduction were measured by the aid of a single electrode (preferably platinised platinum electrode, 2 cm.^{2}) against a saturated calomel reference electrode. Quick equilibria were obtained only when working at 80°. After each process of reduction, samples were taken for analysis for both quadri- and sexa-valent uranium, by means of potassium iodate titration and gravimetric determination of total uranium as U_3O_8. The results showed clearly that reduction to the quadrivalent state proceeded almost to completion as shown by the one inflection in each of the time–potential curves and also by the amount of potassium iodate required for the back titration to the sexavalent state. The reduction proceeded with slight polarisation, the extent of which decreased with increasing acidity up to 4M-HCl. At higher acidity (6·5—7·5M-HCl), the process proceeded with somewhat greater polarisation, accompanied by the deposition of thin grey films on the cathode, especially at high current density. Owing to the formation of these diaphragms, the yield was only about 98% of the theoretical value. However, the reduced solutions were found by analysis to contain mainly quadrivalent uranium. Solutions investigated were always made of 173 ml. of uranyl solution containing 10·9800 g. of U_3O_8 per litre. The acidity varied between 2 and 7·5M-HCl. The applied current density varied between about 2 and 20 milliamp./cm.^{2} of the cathode. In all cases, experiments were carried out at 80° and catholytes were stirred equally.

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78. *Carcinogenic Nitrogen Compounds. Part XIV.* Friedel–Crafts Reactions with* m- *and* p-*Fluorotoluene.*

By NG. PH. BUU-HOÏ and NG. D. XUONG.

The behaviour of *m*- and *p*-fluorotoluene in Friedel–Crafts acylations has been studied. With the former, the reaction is rigidly proved to involve the position *para* to the fluorine atom, and with the latter, the ketone groups are assumed by analogy to occupy the position *ortho* to fluorine. Numerous other aromatic and heterocyclic fluorine-containing compounds have been prepared.

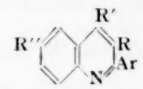
m-CHLORO- and *m*-BROMO-TOLUENE undergo acetylation (Claus, *J. pr. Chem.*, 1891, **43**, 361) and chloroacetylation (Kunckell, *Ber.*, 1908, **41**, 2648) at the position *para* to the halogen atom. We have now found *m*-fluorotoluene to be readily acetylated in a Friedel–Crafts reaction; the constitution of the product as 4-fluoro-2-methylacetophenone was proved by conversion into its oxime, Beckmann rearrangement, and hydrolysis to 4-fluoro-2-methylaniline, prepared from 4-fluoro-2-methyl-1-nitrobenzene (Schiemann, *Ber.*, 1929, **62**, 1797). The constitution of 4-fluoro-2-methyl-propiophenone, -*n*-butyrophenone, and -phenylacetophenone was proved similarly. Sodium hypobromite oxidation of 4-fluoro-2-methylacetophenone gave the hitherto unknown 4-fluoro-2-methylbenzoic acid.

Since the fluorine atom predominates over the methyl group in orienting acylation of *m*-fluorotoluene, just as in acetylation of *o*-fluorotoluene (Buu-Hoï and Jacquignon, *J.*, 1952, 4173), and since acetylation of *p*-chloro- and *p*-bromo-toluene occurred mainly at the position *ortho* to the halogen atom (Claus, *J. pr. Chem.*, 1892, **46**, 21, 26; Mayer and Freund, *Ber.*, 1922, **55**, 2052), the acetylation, propionylation, and phenylacetylation of *p*-fluorotoluene probably also occur at this position. Beckmann rearrangement of 2-fluoro-5-methylpropiophenone oxime yielded a base which is probably 2-fluoro-5-methylaniline.

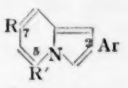
As we are interested in substituted 2-phenylcinchoninic acids, and particularly in the

* Part XIII, *J.*, 1952, 4867.

effect of fluorine therein, we prepared a series of fluorine-containing 2-arylcinchoninic acids (I; R′ = CO_2H), 2-arylquinolines (I; R′ = H) and 2-arylpyrrocolines (II) from the



(I)



(II)

ketones mentioned above. The cinchoninic acids, prepared by Pfitzinger's reaction, are listed in Table 1, and the quinolines obtained by thermal decarboxylation in Table 2. 2-(4-Fluoro-3-methylphenyl)pyrrocoline and its 5- and 7-methyl homologues were prepared from ω-bromo-4-fluoro-2-methylacetophenone and α-picoline or 2 : 4- and 2 : 6-lutidine by Tschitschibabin's reaction (*Ber.*, 1927, **60**, 1607; Borrows, Holland, and Kenyon, *J.*, 1946, 1069, 1075, 1083; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, **68**, 441).

TABLE 1. *Fluorinated cinchoninic acids* (I; R′ = CO_2H).

Subst.				Found, % :		Reqd., % :		Subst.				Found, % :		Reqd., % :	
R	R″	M. p.	Formula	C	H	C	H	R	R″	M. p.	Formula	C	H	C	H
H	H	220°	$C_{17}H_{12}O_2NF$	72·4	4·1	72·6	4·3	H	H	235°	$C_{17}H_{12}O_2NF$	72·4	4·2	72·6	4·3
H	Br	240	$C_{17}H_{11}O_2NBrF$	56·4	3·2	56·7	3·1	H	Me	234	$C_{18}H_{14}O_2NF$	73·0	4·7	73·2	4·7
H	Me	230	$C_{18}H_{14}O_2NF$	73·0	4·8	73·2	4·7	H	Cl	238	$C_{17}H_{11}O_2NClF$	64·4	3·6	64·7	3·5
Me	Me	329	$C_{19}H_{16}O_2NF$	73·5	5·4	73·8	5·2	H	Br	246	$C_{17}H_{11}O_2NBrF$	56·5	3·2	56·7	3·1
Me	H	306	$C_{18}H_{14}O_2NF$	73·1	5·0	73·2	4·7	Me	H	291	$C_{18}H_{14}O_2NF$	73·0	4·8	73·2	4·7
Me	Br	309—310	$C_{18}H_{13}O_2NBrF$	57·6	4·0	57·8	3·5	Me	Cl	300	$C_{18}H_{13}O_2NClF$	65·5	3·9	65·6	4·1
								Me	Br	279	$C_{18}H_{13}O_2NBrF$	57·4	3·6	57·8	3·7
Et	H	304	$C_{19}H_{16}O_2NF$	73·5	5·1	73·8	5·2	Ph	H	>320	$C_{23}H_{16}O_2NF$	77·0	4·3	77·3	4·5
Ph	H	314	$C_{23}H_{16}O_2NF$	77·1	4·3	77·3	4·5	Ph	Cl	312	$C_{23}H_{15}O_2NClF$	70·6	3·9	70·8	3·8
Ph	Br	318	$C_{23}H_{15}O_2NBrF$	63·0	3·2	63·3	3·4	Ph	Br	>320	$C_{23}H_{15}O_2NBrF$	63·0	3·2	63·3	3·4
Ph	Me	>330	$C_{24}H_{18}O_2NF$	77·3	4·8	77·6	4·9								

TABLE 2. (a) *Fluorinated 2-arylquinolines* (I; R′ = H).

Subst.				Found, % :		Reqd., % :		Subst.				Found, % :		Reqd., % :	
R	R″	M. p.	Formula	C	H	C	H	R	R″	M. p.	Formula	C	H	C	H
Ar = 4-Fluoro-2-methylphenyl.								Ar = 2-Fluoro-5-methylphenyl.							
H	Br	118°	$C_{16}H_{11}NBrF$	60·6	3·6	60·8	3·5	H	Br	72°	$C_{16}H_{11}NBrF$	60·5	3·5	60·8	3·5
Me	Br	130	$C_{17}H_{13}NBrF$	61·6	4·2	61·8	3·9	Me	H	80	$C_{17}H_{14}NF$	81·1	5·4	81·3	5·6
Ph	Br	136	$C_{22}H_{15}NBrF$	67·1	4·0	67·3	3·8	Me	Cl	128	$C_{17}H_{13}NClF$	71·2	4·4	71·4	4·5
								Me	Br	132	$C_{17}H_{13}NBrF$	61·5	3·6	61·8	3·9
Ar = 2-Fluoro-5-methylphenyl.								Ph	H	130	$C_{22}H_{16}NF$	84·0	5·2	84·3	5·1
H	Cl	73	$C_{16}H_{11}NClF$	70·4	4·2	70·7	4·0	Ph	Br	154	$C_{22}H_{15}NBrF$	67·0	3·5	67·3	3·8

(b) *Picrates of fluorinated 2-arylquinolines* (I; R′ = H).

Subst.				Found, %:	Reqd., %:	Subst.				Found, %:	Reqd., %:
R	R″	M. p.	Formula	N	N	R	R″	M. p.	Formula	N	N
Ar = 4-Fluoro-2-methylphenyl.						Ar = 2-Fluoro-5-methylphenyl.					
H	H	190°	$C_{22}H_{15}O_7N_4F$	12·0	11·7	H	Cl	195°	$C_{22}H_{14}O_7N_4ClF$	11·2	11·0
Ph	Br	182	$C_{28}H_{18}O_7N_4BrF$	9·0	9·2	H	Br	207	$C_{22}H_{14}O_7N_4BrF$	10·3	10·0
						Me	H	192	$C_{23}H_{17}O_7N_4F$	11·7	11·3
Ar = 2-Fluoro-5-methylphenyl.						Me	Cl	194	$C_{23}H_{16}O_7N_4ClF$	10·9	10·6
H	Me	210	$C_{23}H_{17}O_7N_4F$	11·7	11·4	Me	Br	185	$C_{23}H_{16}O_7N_4BrF$	10·0	10·2
Me	Me	171	$C_{24}H_{19}O_7N_4F$	11·3	11·5	Ph	H	216	$C_{28}H_{19}O_7N_4F$	10·3	10·0
H	H	198	$C_{22}H_{15}O_7N_4F$	12·0	12·3						

EXPERIMENTAL

4-Fluoro-2-methylacetophenone.—A mixture of *m*-fluorotoluene (30 g.) and acetyl chloride (24 g.), in dry carbon disulphide (100 c.c.), and powdered aluminium chloride (48 g.), was kept at room temperature for 24 hours and subsequently refluxed for 2 hours. After the usual treatment, the ketone was obtained as a mobile liquid (40 g.), b. p. 206°, n_D^{20} 1·5120 (Found: C, 71·0; H, 5·8. C_9H_9OF requires C, 71·1; H, 5·9%); *oxime*, prisms (from ether), m. p. 88° (Found: N, 8·1. $C_9H_{10}ONF$ requires N, 8·4%); p-*dimethylaminobenzylidene* derivative, long, orange-yellow needles (from methanol), m. p. 109° (Found: N, 4·9. $C_{18}H_{18}ONF$ requires N, 4·9%).

4-Fluoro-2-methylbenzoic Acid.—4-Fluoro-2-methylacetophenone (19 g.) was shaken with aqueous sodium hypobromite (from bromine, 21·4 c.c.; sodium hydroxide, 42 g.); the resulting bromoform was decanted, and the excess of hypobromite destroyed by sodium hydrogen sulphite. Acidification with hydrochloric acid precipitated the *acid*, which formed silky sublimable needles (from benzene), m. p. 168° (Found: C, 62·0; H, 4·6. $C_8H_7O_2F$ requires C, 62·3; H, 4·5%).

4-Fluoro-2-methylaniline.—To an ice-cooled solution of 4-fluoro-2-methylacetophenone oxime (9 g.) in anhydrous ether (100 c.c.), finely powdered phosphorus pentachloride (12 g.) was added with shaking (15 min.). The mixture was poured on ice, the ethereal layer washed with water, the solvent removed, and the residue refluxed for 1 hour with concentrated hydrochloric acid. The amine obtained on basification was taken up in benzene and purified by vacuum-distillation; it formed a pale yellow oil (4 g.), b. p. 90—92°/16 mm., n_D^{23} 1·5335, which gave a picrate, m. p. 199°, and an *N*-benzoyl derivative, m. p. 165—166° (Schiemann, *loc. cit.*, gave m. p. 199° and 166°, respectively).

4-Fluoro-2-methylpropiophenone.—This *ketone*, obtained in 80% yield as for the lower homologue, had b. p. 220° (119°/13 mm.), n_D^{20} 1·5081 (Found: C, 71·1; H, 6·6. $C_{10}H_{11}OF$ requires C, 72·3; H, 6·6%). *4-Fluoro-2-methyl-n-butyrophenone* (85% yield) formed a pale yellow liquid, b. p. 233° (135°/13 mm.), n_D^{20} 1·5005 (Found: C, 73·3; H, 7·5. $C_{11}H_{13}OF$ requires C, 73·3; H, 7·2%); its *oxime* was a pale yellow oil, b. p. 155°/18 mm., n_D^{25} 1·5172 (Found: N, 7·0. $C_{11}H_{14}ONF$ requires N, 7·2%), which underwent a Beckmann rearrangement to give the same amine as above. *4-Fluoro-2-methyl-α-phenylacetophenone* had b. p. 308° (196°/14 mm.), n_D^{20} 1·5630 (Found: C, 78·8; H, 5·8. $C_{15}H_{13}OF$ requires C, 78·9; H, 5·7%), giving a *thiosemicarbazone*, m. p. 138° (Found: N, 13·7. $C_{16}H_{16}N_3SF$ requires N, 14·0%).

2-(4-Fluoro-2-methylphenyl)pyrrocoline (II; R = R′ = H).—ω-Bromo-4-fluoro-2-methylacetophenone, prepared from 4-fluoro-2-methylacetophenone (10·5 g.) and bromine (11 g.), had b. p. 140°/15 mm., n_D^{18} 1·5603. A solution of this compound (1·5 g.) and α-picoline (0·6 g.) in ethanol (10 c.c.) was refluxed for 30 min.; on addition of ether, a precipitate of the acylpyridinium salt was obtained, and this was collected and treated with a boiling aqueous solution of sodium hydrogen carbonate for 10 min.; the *pyrrocoline* obtained formed from ethanol fine, shiny prisms (1 g.), m. p. 86° (Found: C, 79·8; H, 5·5. $C_{15}H_{12}NF$ requires C, 80·0; H, 5·3%). *2-(4-Fluoro-2-methylphenyl)-7-methylpyrrocoline* (II; R = Me, R′ = H), similarly prepared from 2 : 4-lutidine (0·8 g.), formed from ethanol shiny leaflets, m. p. 74° (Found: C, 80·1; H, 6·1. $C_{16}H_{14}NF$ requires C, 80·3; H, 5·9%). The analogous *5-methylpyrrocoline* (II; R = H, R′ = Me), prepared from 2 : 6-lutidine, was an oil (Found: N, 6·1. $C_{16}H_{14}NF$ requires N, 5·9%), and gave a *picrate* as brownish prisms (from ethanol), m. p. 155—156° (Found: N, 12·2. $C_{22}H_{17}O_7N_4F$ requires N, 12·0%).

2-Fluoro-5-methylacetophenone.—Obtained from *p*-fluorotoluene (35 g.) as a liquid (20 g.), b. p. 208—209°, n_D^{21} 1·5090 (Found: C, 71·1; H, 6·0. C_9H_9OF requires C, 71·1; H, 5·9%), this *ketone* formed a p-*dimethylaminobenzylidene* derivative, shiny yellow leaflets, m. p. 99° (Found: N, 4·6. $C_{18}H_{18}ONF$ requires N, 4·9%), from methanol.

2-Fluoro-5-methylpropiophenone.—The *ketone*, obtained in 78% yield, had b. p. 22°, n_D^{21} 1·4999 (Found: C, 72·2; H, 7·4. $C_{10}H_{11}OF$ requires C, 72·3; H, 7·2%); its *oxime*, a viscous oil, b. p. 150°/18 mm., $n_D^{25\cdot5}$ 1·5268 (Found: N, 7·5. $C_{10}H_{12}ONF$ requires N, 7·7%), gave on Beckmann rearrangement *2-fluoro-5-methylaniline*, a pale yellow oil, b. p. 88—90°/17 mm., n_D^{23} 1·5312 (Found: C, 67·1; H, 6·2. C_7H_8NF requires C, 67·2; H, 6·4%); its *N-acetyl* derivative crystallised from ligroin–benzene as silky leaflets, m. p. 70° (Found: C, 64·6; H, 6·2. $C_9H_{10}ONF$ requires C, 64·7; H, 6·07.). *2-Fluoro-5-methyl-α-phenylacetophenone*, obtained in 75% yield, was a pale yellow oil, b. p. 316° (204—206°/17 mm.), n_D^{21} 1·5600 (Found: C, 78·6; H, 5·7. $C_{15}H_{13}OF$ requires C, 78·9; H, 5·7%).

Pfitzinger Reactions.—These were performed as described by Buu-Hoï (*J.*, 1946, 795). The cinchoninic *acids* (Table I) obtained were recrystallised from ethanol or acetic acid; the corresponding *quinolines* (Table 2*a*) were prepared by heating the well-dried acids above their m. p. in a vacuum, distilling the residue, and crystallising the distillate from ethanol.

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79. *Alicyclic Glycols. Part VIII.** 1 : 2-*Bishydroxymethyl*cyclo*hexane.*

By G. A. Haggis and L. N. Owen.

Reduction of *cis*- or *trans*-hexahydrophthalic ester with lithium aluminium hydride occurs without epimerisation, and gives, respectively, *cis*- or *trans*-1 : 2-bishydroxymethyl*cyclo*hexane (I); the *trans*-isomer has been resolved through the bis-(−)-menthylurethane. Cyclodehydration to octahydro*iso*benzofuran (II) occurs very readily when the diol is treated under mild conditions with dehydrating agents; (II) is also obtained by hydrolysis of the dimethanesulphonates with aqueous alkali, and is formed as a by-product in the preparation of the disulphonyl esters from the diol, and in certain other reactions. From the diol of appropriate configuration, (II) has been prepared in *cis*- (II*a*), *trans*- (II*b*), and (+)-*trans*-forms. Fission of the tetrahydrofuran ring in (II*a* and *b*) has been effected with hydrogen bromide, acetyl chloride, acetyl bromide, *p*-nitrobenzoyl bromide, and toluene-*p*-sulphonyl chloride, and the structures of the products have been established.

The regeneration of some alcohols by reductive fission of their urethanes with lithium aluminium hydride is reported.

1 : 2-Bishydroxymethyl*cyclo*hexane (I) was first prepared, in poor yield and accompanied by the intramolecular ether, octahydro*iso*benzofuran (II), by reduction of diethyl hexahydrophthalate with sodium and alcohol (Wieland, Schlichtling, and Langsdorff, *Z. physiol. Chem.*, 1926, **161**, 74). It was later obtained as a minor product from the hydrogenation of the hexahydro-ester over a chromite catalyst at 385° (U.S.P. 2,105,664), the main reaction then being hydrogenolysis to 2-methyl*cyclo*hexylmethanol. In our hands, Bouveault–Blanc reduction of dimethyl hexahydrophthalate has given the diol in 68% yield, with only a small amount of cyclic oxide, and as Wieland *et al.* recovered much hexahydrophthalic acid in their experiments it is probable that their low yield of diol was due to use of imperfectly dried alcohol. By precipitation with light petroleum and recrystallisation from benzene, they obtained a solid, m. p. 57°, but its configuration was not established.

Although in the present work only 14% of the diol was obtained in this solid form, it was shown by preparation of derivatives that the non-crystallisable portion also consisted mainly of this isomer. The hexahydro-ester used in the reduction had been prepared by hydrogenation of dimethyl phthalate, and was probably largely the *cis*-form (cf. Price and Schwarcz, *J. Amer. Chem. Soc.*, 1940, **62**, 2891), but it does not follow that the composition of the resulting diol would be similar because under the Bouveault–Blanc conditions it is likely that a considerable proportion of the *cis*- would isomerise to *trans*-ester before reduction occurred. Noyce and Denney (*ibid.*, 1950, **72**, 5743) found that reduction of (+)-α-methylbutyric acid with lithium aluminium hydride gave (−)-2-methylbutanol with complete retention of configuration; with sodium and alcohol such a reaction would certainly have resulted in partial or complete racemisation, and the newer method, if of general application, will provide a valuable means of correlating the configuration of alcohols with the corresponding acids in cases where the α-carbon atom is involved in the stereoisomerism. Accordingly, we studied the reduction by lithium aluminium hydride of dimethyl *trans*-hexahydrophthalate. The product, obtained in excellent yield, crystallised completely and was identical with the solid, m. p. 57°, which consequently must be the *trans*-diol. Similar reduction of *cis*-hexahydrophthalic anhydride and of *cis*-diethyl hexahydrophthalate gave a stereochemically pure diol, m. p. 42—43°, which must be the *cis*-isomer. The stereo-specificity of the method is therefore established. Independent confirmation was provided by resolution of the *trans*-diol and isolation of the (+)-form, m. p. 61—62°, $[\alpha]_D^{24}$ +21°.

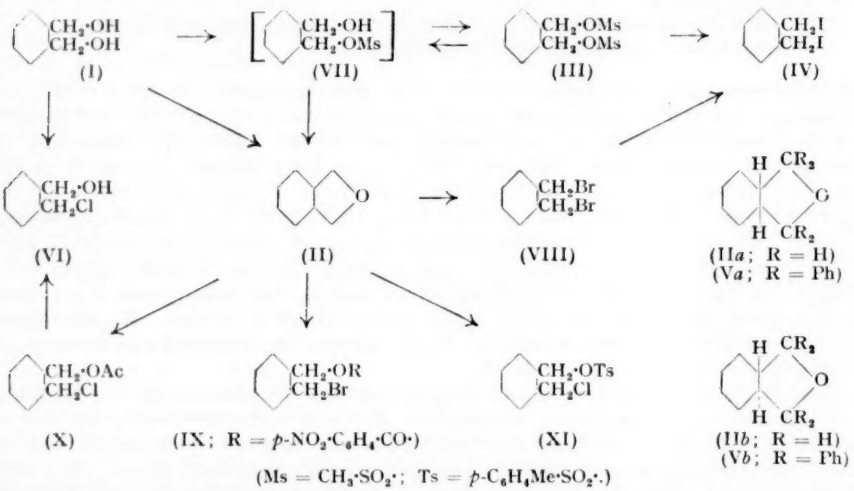
Reaction of the *trans*-diol with (−)-menthoxyacetyl chloride gave an oily menthoxy-

* Part VII, Owen and Smith, *J.*, 1952, 4035.

acetate. Preparation of the acid sulphate was not attempted since the diol was readily dehydrated by cold sulphuric acid. The di(acid phthalate) was prepared as a solid but no crystalline alkaloid salts could be obtained. The resolution was finally accomplished by use of (−)-menthyl *iso*cyanate. This comparatively inaccessible resolving agent was prepared first by Neville and Pickard (*J.*, 1904, **85**, 688) by dehydration of ethyl (−)-menthylcarbamate, and later (Vallée, *Ann. Chim.*, 1908, **15**, 410; Tschugaeff and Glebko, *Ber.*, 1913, **46**, 2759) by reaction of (−)-menthylamine hydrochloride with carbonyl chloride in toluene at 140—150°; a modification of the latter method was used in the present work.

The diols were characterised by preparation of several derivatives. The yields of ditoluene-*p*-sulphonates and dimethanesulphonates (III) were not as good as expected; this was traced to the simultaneous formation of the cyclic oxide (see p. **391**).

The *cis*- and *trans*-dimethanesulphonates and ditoluene-*p*-sulphonates reacted with sodium iodide in boiling acetone to give the *cis*- and the *trans*-1 : 2-bisiodomethyl*cyclo*hexane (IV); the *trans*-isomers reacted more rapidly than the *cis*-, the difference being more marked with the toluene-*p*-sulphonates and clearly being due to variation in the degree of steric hindrance.



Examination of scale models shows that both the *cis*- and the *trans*-diol can take up strainless conformations in which the two hydroxyl groups are near to one another, and Dr. L. P. Kuhn, who kindly determined the infra-red spectra of the two isomers (*J. Amer. Chem. Soc.*, 1952, **74**, 2492), reported that both showed strong intramolecular hydrogen bonding in solution. Wittig and Waltnitzki (*Ber.*, 1934, **67**, 667) had already shown that the *cis*- and the *trans*-tetraphenyl-substituted diols, which they prepared by reaction of diethyl *cis*- and *trans*-hexahydrophthalates with phenyl-lithium, gave on dehydration the *cis*-(V*a*) and the *trans*-(V*b*) tetraphenyl-substituted octahydro*iso*benzofuran. It was to be expected, therefore, that octahydro*iso*benzofuran would also exist in two stereoisomeric forms (II*a*) and (II*b*).

Preliminary experiments, carried out with the mixture of *cis*- and *trans*-1 : 2-bishydroxymethyl*cyclo*hexane obtained by Bouveault–Blanc reduction, showed that dehydration to the cyclic oxide occurred under mild conditions, such as treatment with sulphuric acid in cold acetone or boiling under reflux with methanolic hydrogen chloride. Octahydro*iso*benzofuran was also obtained, accompanied by unsaturated material, by dehydration over alumina at 200—250°.

Other than direct dehydration, the most usual method for preparation of intramolecular ethers involves interaction of a monohalide or monosulphonyl ester with alkali.

Attempted preparation of the monochloride (VI) by reaction of the *trans*-diol with fuming hydrochloric acid gave a mixture of the required compound and the oxide. The monochloride decomposed slightly on distillation under reduced pressure, and rapidly at 200°, with evolution of hydrogen chloride and formation of the oxide. 4-Chlorobutanol is similarly unstable to distillation (Bennett and Heathcoat, *J.*, 1929, 268). Attempts to prepare the monotoluene-*p*-sulphonate by slow reaction of a dilute solution of the *trans*-diol in pyridine with 1 mol. of the acid chloride were unsuccessful, some ditoluene-*p*-sulphonate and cyclic oxide being formed. Reaction of the *trans*-monochloride with a suspension of silver toluene-*p*-sulphonate in benzene gave the oxide as the only identifiable product.

Since a pure monotoluene-*p*-sulphonate could not be obtained, the hydrolysis of the disulphonates was studied. Reaction of a primary sulphonate group with alkali normally leads to hydrolysis (in aqueous solution) or to solvolysis (in alcoholic solution); aqueous hydrolysis of a disulphonate of the type (III) should therefore give a monosulphonate (VII) as an intermediate, which under the alkaline conditions would be expected to form (II). The *trans*-ditoluene-*p*-sulphonate was unaffected by boiling aqueous potassium hydroxide, probably because of its insolubility, and with the methanolic reagent it gave mainly the dimethyl ether of the *trans*-diol. Similar resistance to hydrolysis by aqueous alkali has been noted by Newth and Wiggins (*J.*, 1948, 155) for the ditoluene-*p*-sulphonate of 2 : 5-bishydroxymethyltetrahydrofuran. Dimethanesulphonates, however, are usually rather more soluble in aqueous solution, and would be expected to be more reactive. This was found to be so, and the *cis*-derivative (III) when boiled for 3 hours with aqueous potassium hydroxide gave *cis*-octahydro*iso*benzofuran in 60% yield. Similar treatment of *trans*-(III) gave *trans*-octahydrobenzofuran, and from the (−)-*trans*-dimethanesulphonate there was obtained (+)-*trans*-octahydro*iso*benzofuran, $[\alpha]_D^{22}$ +110°.

The low yields obtained in the preparation of the sulphonyl esters were explained when it was found that from a large-scale preparation the oxide could be isolated as a by-product. With the *trans*-diol, 10% was recovered as oxide after toluene-*p*-sulphonation; methanesulphonation of the *cis*-diol gave 31% of the *cis*-oxide and only 32·5% of the dimethanesulphonate. It is clear that in these reactions the intermediate monosulphonate (*e.g.*, VII) reacts in two ways, either with more acid chloride to give the disulphonate (III), or with loss of sulphonic acid under the influence of pyridine to give the oxide (II), and this was supported by the observation that if the acid chloride was added in one portion to a solution of the diol in pyridine, or if the diol was added slowly to the acid chloride in pyridine (rather than the usual procedure of gradual addition of the acid chloride to the diol in pyridine) the yield of dimethanesulphonate was increased as a consequence of the higher initial concentration of acid chloride. The instability of the intermediate monoester in the presence of pyridine accounts for the lack of success in the attempted preparation of the monotoluene-*p*-sulphonate.

The formation of the cyclic oxide in this reaction is formally analogous to the conversion of a 1 : 4- or 1 : 5-diol into the corresponding tetrahydro-furan or -pyran by treatment with 1 mol. of a sulphonyl chloride in boiling pyridine or 2 : 6-lutidine (Reynolds and Kenyon, *J. Amer. Chem. Soc.*, 1950, **72**, 1593), which probably proceeds through the intermediate monosulphonate. There have been no previous reports, however, of such a cyclisation occurring at low temperatures, and we therefore studied the methanesulphonation of butane-1 : 4-diol (from which, with benzenesulphonyl chloride and boiling pyridine, Reynolds and Kenyon had obtained 35% of tetrahydrofuran) under the same conditions as were used for the alicyclic diol. The dimethanesulphonate was obtained in excellent yield, and no tetrahydrofuran could be detected; it follows that cyclisation under mild conditions is not general, and probably occurs with 1 : 2-bishydroxymethyl*cyclo*hexane because of the favourable disposition of the hydroxyl groups. Reaction of the dimethanesulphonate of butane-1 : 4-diol with boiling aqueous alkali gave tetrahydrofuran in 58% yield.

Octahydro*iso*benzofuran was soluble in concentrated sulphuric acid, and was recovered unchanged on dilution with water. Although stable to neutral potassium permanganate it was rapidly oxidised in the cold by the alkaline reagent, or on heating with the acid

reagent. The *trans*-isomer gave an insoluble complex with hydroferricyanic acid, similar to that formed by 1 : 8-cineole (Baeyer and Villiger, *Ber.*, 1901, **34**, 2690); the oxide was regenerated by treatment with sodium hydrogen carbonate solution. The boiling point and refractive index of the *cis*-oxide were slightly higher than those of the *trans*-isomer, but the two forms were best differentiated by conversion into crystalline derivatives by fission of the heterocyclic ring by use of some of the reagents known to be effective with tetrahydrofuran systems (cf. Owen, *Ann. Reports*, 1945, **42**, 171; Jones and Taylor, *Quart. Reviews*, 1950, **4**, 195; Clarke and Owen, *J.*, 1950, 2109). Reaction with acetic anhydride and zinc chloride gave only a poor yield of an impure diacetate, with much polymeric material. Reaction of the *trans*-oxide with hydrogen bromide at 90° gave the *trans*-dibromide (VIII) in good yield; this was converted into the *trans*-di-iodide (IV) by reaction with sodium iodide in acetone, and into the *trans*-diol by reaction with potassium acetate and silver acetate, followed by deacetylation. Ring-fission had therefore occurred normally, without affecting the configuration. Similarly, reaction of the *cis*- and the *trans*-oxide with *p*-nitrobenzoyl bromide (conveniently prepared by treatment of the readily available chloride with hydrogen bromide), in the presence of zinc chloride, gave the *cis*- and the *trans*-2-bromomethyl*cyclo*hexylmethyl *p*-nitrobenzoate (IX); although these had almost identical melting points, 79° and 81° respectively, the mixed m. p. showed a large depression, and there is no doubt that each was a stereoisomeric individual.

The *trans*-oxide reacted rapidly with acetyl chloride, without a catalyst, to give *trans*-2-chloromethyl*cyclo*hexylmethyl acetate (X), which on deacetylation gave the *trans*-monochloride (VI). With acetyl bromide, the *cis*- and the *trans*-oxide similarly gave the corresponding 2-bromomethyl*cyclo*hexylmethyl acetates, which on deacetylation and *p*-nitrobenzoylation gave products (IX) identical with those from the direct reaction of the oxides with *p*-nitrobenzoyl bromide. *trans*-2-Bromomethyl*cyclo*hexylmethyl acetate reacted slowly with sodium iodide in boiling acetone, but the iodo-compound could not be obtained pure, though on deacetylation and *p*-nitrobenzoylation it gave crystalline *trans*-2-iodomethyl*cyclo*hexylmethyl *p*-nitrobenzoate. Reaction of the *trans*-oxide with toluene-*p*-sulphonyl chloride, catalysed by zinc chloride, furnished a product which was mainly 2-chloromethyl*cyclo*hexylmethyl toluene-*p*-sulphonate (XI).

Entel, Ruof, and Howard (*J. Amer. Chem. Soc.*, 1952, **74**, 441) obtained octahydro*iso*benzofuran, probably as a mixture of *cis*- and *trans*-forms, by hydrogenation of phthalan, but did not describe its reactions.

In connection with the resolution of the *trans*-diol, incidental experiments were carried out on the regeneration of alcohols from their urethanes. It was found that methyl phenylcarbamate was smoothly and rapidly reduced by lithium aluminium hydride in boiling ether to *N*-methylaniline (no attempt was made to isolate the regenerated methanol). The bis-(−)-menthylurethane of the *trans*-diol similarly gave the *trans*-diol and *N*-(−)-menthylmethylamine. The (−)-menthylurethane of (−)-menthol was more resistant, and only a small yield of (−)-menthol was obtained, most of the derivative being recovered unchanged (a higher-boiling solvent might have been advantageous). Read and Roebuck (*J.*, 1952, 812) failed to hydrolyse this compound with boiling alcoholic potassium hydroxide, although the corresponding phenylurethane was readily attacked. Salmon and Powell (*J. Amer. Chem. Soc.*, 1939, **61**, 3507) reported the regeneration of 5 : 6-dimethyl 1 : 2-*iso*propylidene glucose from its phenylurethane by reaction with boiling methanolic sodium methoxide, but the bis-(−)-menthylurethane of our *trans*-diol was unaffected by this treatment, although fission was smoothly effected with alcoholic potassium hydroxide.

Experimental

p-Nitrobenzoyl Bromide.—A stream of dry hydrogen bromide was passed through molten *p*-nitrobenzoyl chloride at 100°. After 4 hours the evolved gas contained no hydrogen chloride; the product crystallised from carbon tetrachloride as yellow needles, m. p. 64°. Adams and Ulich (*J. Amer. Chem. Soc.*, 1920, **42**, 599) recorded m. p. 63—64°.

(−)-*Menthyl* iso*Cyanate.*—Carbonyl chloride was passed through a suspension of (−)-menthylamine hydrochloride (65 g.) in boiling xylene (400 c.c.) until no more hydrogen chloride was evolved (*ca.* 3 hours). Removal of xylene and distillation of the residue gave (−)-menthyl

*iso*cyanate (58 g.) as a colourless oil, b. p. 77—80°/1 mm., n_D^{22} 1·4605, $[\alpha]_D^{22}$ −64·2° (*c*, 5 in benzene). Vallée (*loc. cit.*) recorded $[\alpha]_D$ −61·89°.

Dimethyl Hexahydrophthalate.—Dimethyl phthalate (200 g.), in methanol (300 c.c.), was hydrogenated at 50—60°/100 atm. over Raney nickel (25 g.) until uptake was complete (*ca.* 24 hours). After filtration and removal of solvent, the ester was distilled (196 g.), b. p. 104—109°/2 mm., n_D^{20} 1·4590. The *trans*-dimethyl ester was prepared from this *cis–trans*-mixture by treatment with methanolic sodium methoxide (cf. Price and Schwarcz, *loc. cit.*). *cis*-Hexahydrophthalic anhydride and *cis*-diethyl hexahydrophthalate were prepared by the method of Price and Schwarcz (*loc. cit.*).

1 : 2-*Bishydroxymethyl*cyclo*hexane.*—(i) Dimethyl hexahydrophthalate (150 g.), in dry ethanol (3 l.), was reduced at reflux temperature with sodium (300 g.) added in portions. When the reaction had moderated, the temperature was kept at 160° (bath) until all the sodium had dissolved. Water (500 c.c.) was then added, and most of the alkali neutralised with 20% sulphuric acid (*ca.* 1200 c.c.). The solution was then cooled and filtered from sodium sulphate, and alcohol removed by distillation. The diol was isolated by continuous extraction of the residual aqueous solution with ether. The ethereal solution was dried (K_2CO_3) and evaporated, and the residue distilled to give 1 : 2-bishydroxymethyl*cyclo*hexane (73·5 g., 68%) as a colourless, viscous oil, b. p. 110—130°/0·3 mm., n_D^{20} 1·4914. A small quantity of a water-insoluble oil was obtained from the liquid-air trap after distillation. This was dried (K_2CO_3) and distilled to give octahydro*iso*benzofuran (0·3 g.), b. p. 69—70°/15 mm., n_D^{19} 1·4678. Fractional distillation of the alcoholic distillate did not yield any more of this material.

The diol (73 g.) was dissolved in benzene (50 c.c.) and stored at 0°; *trans*-1 : 2-bishydroxymethyl*cyclo*hexane, which was slowly deposited, recrystallised from benzene–light petroleum (b. p. 60—80°) as small plates (10 g.), m. p. 57°. Wieland *et al.* (*loc. cit.*) gave m. p. 57°. The mother-liquors on evaporation gave a viscous oil, which was shown to be principally the *trans*-isomer by preparation of the ditoluene-*p*-sulphonate (see below).

(ii) *trans*-Dimethyl hexahydrophthalate (20 g.) in dry ether (40 c.c.) was added slowly to a cooled, stirred solution of lithium aluminium hydride (4·5 g.) in dry ether (200 c.c.). After 1 hour, dilute sulphuric acid was added until all solid had dissolved, and the aqueous layer was separated and continuously extracted with ether. The combined ethereal solutions were dried (K_2CO_3) and evaporated to a yellow oil (13·5 g., 94%) which soon solidified and had m. p. 53—54°. One crystallisation from benzene–light petroleum (b. p. 60—80°) gave the pure *trans*-diol, m. p. and mixed m. p. 57°.

(iii) Similar reduction of *cis*-diethyl hexahydrophthalate (52 g.) in ether (100 c.c.) with lithium aluminium hydride (11 g.) in ether (500 c.c.) gave a yellow oil (30·9 g., 94%) which solidified and had m. p. 37—41°. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave cis-1 : 2-*bishydroxymethyl*cyclo*hexane*, m. p. 42—43° (Found: C, 66·6; H, 11·2. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%); on admixture with the *trans*-diol, it liquefied.

(iv) Similar reduction of *cis*-hexahydrophthalic anhydride (31 g.) with lithium aluminium hydride (8 g.) in ether gave the *cis*-diol (18·3 g., 63%), m. p. and mixed m. p. 41—42°.

Derivatives of the cis-*Diol.*—The *cis*-diol (2·3 g.) and toluene-*p*-sulphonyl chloride (6·7 g.) in pyridine (30 c.c.) at 0° (overnight) gave the cis-*ditoluene*-p-*sulphonate* (3·9 g., 54%), needles (from methanol), m. p. 84—85° (Found: C, 58·2; H, 6·3; S, 14·3. $C_{22}H_{28}O_6S_2$ requires C, 58·4; H, 6·2; S, 14·2%). A similar procedure was used for the cis-*dimethanesulphonate*, needles (57%) (from methanol), m. p. 75—76° (Found: C, 40·2; H, 6·9; S, 21·0. $C_{10}H_{20}O_6S_2$ requires C, 40·0; H, 6·7; S, 21·35%), and for the cis-*di*-p-*nitrobenzoate*, a pale yellow powder (90%) (from acetone–ethanol), m. p. 142° (Found: C, 59·7; H, 5·1; N, 6·4. $C_{22}H_{22}O_8N_2$ requires C, 59·7; H, 5·0; N, 6·3%).

The *cis*-diol (0·5 g.) and phenyl *iso*cyanate (1 g.) at 100° (1 hour) gave the cis-*bisphenylurethane* (1·15 g., 87%) [from benzene–light petroleum (b. p. 60—80°)], m. p. 102° (Found: C, 69·3; H, 6·8; N, 7·5. $C_{28}H_{26}O_4N_2$ requires C, 69·1; H, 6·8; N, 7·3%).

Derivatives of the trans-*Diol.*—By the methods used for the *cis*-derivatives, there were prepared the trans-*ditoluene*-p-*sulphonate* (48%), stout needles (from methanol), m. p. 108° (Found: C, 58·9; H, 6·5; S, 13·9. $C_{22}H_{28}O_6S_2$ requires C, 58·4; H, 6·2; S, 14·2%), the trans-*dimethanesulphonate* (84%), fluffy needles (from methanol), m. p. 92° (Found: C, 40·3; H, 6·9; S, 21·55. $C_{10}H_{20}O_6S_2$ requires C, 40·0; H, 6·7; S, 21·35%), and the trans-*di*-p-*nitrobenzoate* (95%), a yellow powder (from acetone–ethanol), m. p. 168° (Found: C, 60·5; H, 5·2; N, 6·5. $C_{22}H_{22}O_8N_2$ requires C, 59·7; H, 5·0; N, 6·3%) (two further crystallisations from dioxan had no effect on the m. p. or analyses).

When the *trans*-diol (0·5 g.) and phenyl *iso*cyanate (1 g.) were warmed together for a few

minutes, then stored at room temperature for an hour, a solid was obtained which when crystallised from benzene–light petroleum (b. p. 60—80°) gave the trans-*monophenylurethane* (0·85 g., 93%), m. p. 145° (Found : C, 68·5; H, 8·05; N, 5·5. $C_{15}H_{21}O_3N$ requires C, 68·4; H, 8·0; N, 5·3%). Reaction of the same quantities for 3 hours at 100°, however, gave, by similar recrystallisation, the trans-*bisphenylurethane* (1·1 g., 85%), m. p. 139°, depressed to 124° on admixture with the monourethane (Found : C, 69·1; H, 6·95; N, 7·3. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·85; N, 7·3%).

The *trans*-diol (1·33 g.) was heated at 100° with phthalic anhydride (2·7 g.) in pyridine (5 c.c.) for 1 hour. The cooled solution was treated with excess of dilute sulphuric acid, and the precipitated gum was dissolved in chloroform, extracted with sodium carbonate solution, and reprecipitated with acid. It was again dissolved in chloroform, dried (Na_2SO_4), recovered by evaporation, and dissolved in acetone. Addition of light petroleum (b. p. 40—60°) and cooling to 0° gave the *di*(*hydrogen phthalate*) (2·65 g.), m. p. 168—173°, raised to 173—175° by recrystallisation from the same solvent (Found : C, 65·9; H, 5·8. $C_{24}H_{24}O_8$ requires C, 65·5; H, 5·5%). Attempts to form solid salts with strychnine, quinine, and cinchonidine failed.

Derivatives from the Stereoisomeric Mixture of Diols (*mainly* trans).—(i) The diol (1 g.) and acetic anhydride (2·5 g.) were boiled under reflux for 2 hours. The solution was diluted with water, and the ester extracted with chloroform, washed with sodium hydrogen carbonate and water, and dried (Na_2SO_4). Removal of solvent, followed by distillation, gave 1 : 2-*bisacetoxymethyl*cyclo*hexane* as a colourless oil (1·2 g.), b. p. 85—86°/0·2 mm., n_D^{20} 1·4591 (Found : C, 63·05; H, 8·95. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·8%).

(ii) The diol (1 g.) in pyridine (10 c.c.) was treated at 0° with benzoyl chloride (2·5 g.). After 1 hour at 0°, working up as in (i) (with an acid wash) gave 1 : 2-*bisbenzoyloxymethyl*cyclo*hexane* as a viscous oil (1·5 g.), b. p. 210—215° (bath)/7 × 10^{-5} mm. (Found : C, 74·5; H, 6·6. $C_{22}H_{24}O_4$ requires C, 75·0; H, 6·35%).

(iii) The diol (10 g.) in pyridine (30 c.c.) was cooled to 0° and a solution of toluene-*p*-sulphonyl chloride (30 g.) in pyridine (50 c.c.) was added slowly to the stirred solution. After 2 hours water was added to precipitate the toluene-*p*-sulphonate (15 g.). By fractional crystallisation from acetone–methanol this was separated into the *trans*-compound, m. p. 108° (9·5 g.), and the material, m. p. 87—88° (1·7 g.) undepressed on admixture with the *cis*-isomer, m. p. 84—85°, recorded above. The aqueous filtrate from the toluene-*p*-sulphonation was extracted with chloroform, and the extract washed with dilute sulphuric acid and aqueous sodium hydrogen carbonate, and dried (Na_2SO_4). After removal of chloroform, distillation gave octahydro*iso*benzofuran (0·95 g.), b. p. 68°/15 mm., n_D^{15} 1·4705.

Similarly, reaction of the diol (10 g.) in pyridine (50 c.c.) with methanesulphonyl chloride (18 g.) in pyridine (25 c.c.) gave a methanesulphonate (20 g.) which on fractional crystallisation gave the *trans*-compound (13 g.), m. p. 92°, and impure *cis*-isomer, m. p. 72—73° (0·3 g.).

Resolution of trans-1 : 2-*Bishydroxymethyl*cyclo*hexane*.—The *trans*-diol (19 g.) and (−)-menthyl *iso*cyanate (50 g.) in benzene (50 c.c.) were heated at 100° overnight. Benzene was removed under reduced pressure, and the semi-solid residue was dissolved in light petroleum (b. p. 60—80°) containing a little benzene. On cooling, a powdery solid separated (51 g.), having m. p. 110—120°, $[\alpha]_D^{22}$ −57·9° (*c*, 2 in C_6H_6). Fractional crystallisation from light petroleum (b. p. 60—80°), containing a little benzene, and finally from methanol, gave the *bis*-(−)-*menthylurethane* (9·6 g.), m. p. 150—151°, $[\alpha]_D^{20}$ −66·2° (*c*, 2 in C_6H_6) (Found : C, 71·5; H, 10·85; N, 5·8. $C_{30}H_{54}O_4N_2$ requires C, 71·1; H, 10·75; N, 5·5%).

The urethane (9·5 g.) in ethanol (100 c.c.) containing potassium hydroxide (6 g.) was heated under reflux overnight. Ethanol and (−)-menthylamine were removed by steam-distillation, and the diol was isolated by continuous extraction of the residue with ether. Evaporation of the dried extracts, followed by distillation, gave the (+)-trans-*diol* (2·2 g.), b. p. 110—113°/0·2 mm., which rapidly solidified, m. p. 61—62°, unchanged on crystallisation from benzene–light petroleum (b. p. 60—80°), from which it formed needles, $[\alpha]_D^{24}$ +21·4° (*c*, 4 in C_6H_6) (Found : C, 66·6; H, 11·2. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%).

The following derivatives were prepared by methods previously described : *dimethanesulphonate*, m. p. 80—90°, unchanged by recrystallisation, $[\alpha]_D^{24\cdot5}$ −29·2° (*c*, 4 in C_6H_6) (Found : C, 40·0; H, 6·9; S, 21·1. $C_{10}H_{20}O_6S_2$ requires C, 40·0; H, 6·7; S, 21·35%); *ditoluene*-p-*sulphonate*, m. p. 109—110°, $[\alpha]_D^{21\cdot5}$ −24·8° (*c*, 5 in C_6H_6) (Found : C, 58·4; H, 6·4; S, 13·8. $C_{22}H_{28}O_6S_2$ requires C, 58·4; H, 6·2; S, 14·2%); *bisphenylurethane*, m. p. 132—133°, $[\alpha]_D^{22}$ −20·4° (*c*, 3 in $CHCl_3$) (Found : C, 69·5; H, 7·0; N, 7·55. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·85; N, 7·3%).

cis-1 : 2-*Bisiodomethyl*cyclo*hexane*.—(i) The *cis*-ditoluene-*p*-sulphonate (5·2 g.) was boiled

under reflux for 16 hours in acetone (80 c.c.) containing sodium iodide (7·5 g.). Sodium toluene-*p*-sulphonate (3·45 g., 78%) was filtered off, and the solvent removed under reduced pressure. Addition of water to the residue precipitated a heavy oil, which was dissolved in chloroform and washed with sodium thiosulphate solution and with water. Evaporation of the dried (Na_2SO_4) extract and distillation of the residual oil gave cis-1 : 2-*bisiodomethyl*cyclo*hexane* (2·6 g., 62%) as a pale yellow liquid, b. p. 100° (bath)/0·002 mm., n_D^{17} 1·6151 (Found : C, 26·7; H, 3·9; I, 69·1. $C_8H_{14}I_2$ requires C, 26·4; H, 3·9; I, 69·7%).

(ii) The *cis*-dimethanesulphonate (13·7 g.) in boiling acetone (200 c.c.), containing sodium iodide (19 g.), after 5 hours gave sodium methanesulphonate (9·9 g.) and the *cis*-di-iodide (8·9 g., 54%), b. p. 80° (bath)/10^{-4} mm., n_D^{20} 1·6096.

trans-1 : 2-*Bisiodomethyl*cyclo*hexane*.—(i) The *trans*-ditoluene-*p*-sulphonate (25 g.), in boiling acetone (400 c.c.), containing sodium iodide (35 g.), after 2·5 hours gave sodium toluene-*p*-sulphonate (21 g., 100%). The crude trans-1 : 2-*bisiodomethyl*cyclo*hexane* obtained by dilution of the filtrate with water solidified at 0° and crystallised from methanol as needles (14·1 g., 70%), m. p. 39—40° (Found : C, 26·7; H, 3·9; I, 69·6. $C_8H_{14}I_2$ requires C, 26·4; H, 3·9; I, 69·7%).

(ii) The *trans*-dimethanesulphonate (5 g.) in acetone (80 c.c.) containing sodium iodide (7 g.) similarly gave the *trans*-di-iodide (3·05 g., 50%), m. p. and mixed m. p. 39—40°.

Reaction of the trans-*Ditoluene*-p-*sulphonate with Methanolic Potassium Hydroxide*.—The ester (10 g.) was heated under reflux with potassium hydroxide (5 g.) in methanol (100 c.c.) for 3 hours. Potassium toluene-*p*-sulphonate (9·2 g., 99%) was filtered off, and methanol removed by distillation. Water and ether were added, and the ethereal layer was separated, dried (Na_2SO_4), and evaporated; distillation then gave a product (1·87 g.), b. p. 78—93°/12 mm., n_D^{18} 1·4560—1·4505, from which trans-1 : 2-*bismethoxymethyl*cyclo*hexane* was obtained by repeated fractionation, as an oil, b. p. 92—94°/12 mm., n_D^{18} 1·4495 (Found : C, 69·9; H, 11·8. $C_{10}H_{20}O_2$ requires C, 69·7; H, 11·7%).

*Octahydro*iso*benzofuran* (cis + trans).—(i) The liquid diol (10 g.) (mainly *trans*) was dissolved in dry acetone (150 c.c.) containing sulphuric acid (1 c.c.). Anhydrous sodium sulphate was added, and the solution left at room temperature for 48 hours. Acid was neutralised with solid sodium hydrogen carbonate, and, after filtration and removal of acetone, distillation gave octahydro*iso*benzofuran (2·7 g., 31%) as a mobile oil, insoluble in water, and having a terpene-like odour, b. p. 56—57°/7 mm., b. p. 175°/760 mm., n_D^{20} 1·4680. [Wieland *et al.* (*loc. cit.*) gave b. p. 170—175°; Entel, Ruof, and Howard (*loc. cit.*) b. p. 179°/740 mm., n_D^{25} 1·4683.] A similar experiment using ether as solvent instead of acetone gave a much lower yield of oxide. Dehydration of the pure *trans*-diol with acetone and sulphuric acid gave the *trans*-form, b. p. 65—70°/15 mm., n_D^{26} 1·4655.

(ii) A solution of the liquid diol (5 g.) in methanol (50 c.c.) containing 1% of hydrogen chloride was refluxed for 24 hours and then neutralised by sodium hydrogen carbonate solution. The product was extracted with ether, and on distillation gave the oxide (0·85 g., 19%), b. p. 66—70°/12 mm., n_D^{20} 1·4685, and unchanged diol (0·35 g.).

(iii) A mixture of the liquid diol (50 g.) with activated alumina (12 g.) was heated (oil-bath) in a distillation flask. Distillation began at 200° (internal temp.), and the temperature was gradually raised to 250°. The distillate separated into two layers, the upper of which was dried (K_2CO_3) and distilled, the fraction (35 g.) of b. p. 65—90°/15 mm., n_D^{20} 1·4850, being collected. The residue was viscous and probably contained some unchanged diol. The distillate, which was unsaturated, was stirred with saturated magnesium sulphate solution (250 c.c.), and 2% aqueous potassium permanganate was added slowly until a filtered portion remained pink for 10 minutes. The product was isolated from the filtered solution by steam-distillation, and was dried (K_2CO_3) and distilled to give the oxide (22 g., 50%), b. p. 65—66°/9 mm., n_D^{20} 1·4680. Repetition of the experiment on a small scale with the pure *trans*-diol gave similar results.

cis-*Octahydro*iso*benzofuran*.—(i) The *cis*-diol (25 g.) in pyridine (200 c.c.) was cooled to 0° and a solution of methanesulphonyl chloride (44 g.) in pyridine (100 c.c.) was added slowly with stirring. After 2 hours water was added, and the *cis*-dimethanesulphonate was collected and recrystallised from methanol (yield 17 g., 32·5%). The aqueous filtrate was extracted with chloroform, and the chloroform solution was washed with dilute sulphuric acid and sodium hydrogen carbonate, and dried (Na_2SO_4). Removal of chloroform and distillation of the residual oil gave cis-*octahydro*iso*benzofuran* (6·75 g.), b. p. 59°/9 mm., 174—175°/751 mm., n_D^{21} 1·4712 (Found : C, 76·1; H, 11·2. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). A comparative experiment, in which the pyridine solutions were cooled in a freezing mixture, and the acid chloride added all at once, gave a 61% yield of the dimethanesulphonate.

(ii) The *cis*-dimethanesulphonate (55 g.) was boiled under reflux for 3 hours with 15% aqueous potassium hydroxide (300 c.c.). Steam-distillation, and extraction of the distillate with ether, afforded the *cis*-oxide (12·9 g., 56%), b. p. 68—72°/16 mm., n_D^{21} 1·4694. The product was slightly unsaturated. The residue from the distillation (3·5 g.) was strongly unsaturated and probably contained 2-methylene*cyclo*hexylmethanol.

trans-*Octahydroisobenzofuran*.—The *trans*-dimethanesulphonate (23 g.) was boiled under reflux for 3 hours with 15% aqueous potassium hydroxide (150 c.c.). The product was isolated as described above, and on distillation furnished trans-*octahydroisobenzofuran* (5·8 g., 61%), b. p. 75—76°/25 mm., 172·5—173°/751 mm., n_D^{17} 1·4695 (Found: C, 75·8; H, 11·2%). No diol was isolated by continuous ether-extraction of the aqueous residue from the steam-distillation.

When the *trans*-oxide (0·1 g.) was added to a solution of potassium ferricyanide (0·05 g.) in 20% hydrochloric acid (5 c.c.) a yellow precipitate was formed. This complex was filtered off, washed thoroughly with 20% hydrochloric acid, and dried at room temperature in a high vacuum. It could not be recrystallised, and decomposed without melting at 130—150° (Found: C, 52·3; H, 7·0; Fe, 11·9. Calc. for $H_3FeC_6N_6,2C_8H_{14}O$: C, 56·5; H, 7·5; Fe, 11·9%). When it was added to sodium hydrogen carbonate solution effervescence occurred and the oxide was regenerated.

(+)-trans-*Octahydroisobenzofuran*.—Reaction of the (−)-dimethanesulphonate (2 g.) with boiling aqueous potassium hydroxide as described above gave (+)-trans-*octahydroisobenzofuran* (0·34 g.), b. p. 74°/26 mm., n_D^{24} 1·4655, $[\alpha]_D^{22}$ +110° (*c*, 5 in C_6H_6) (Found: C, 76·0; H, 11·2%).

Methanesulphonation of Butane-1 : 4-*diol and Conversion into Tetrahydrofuran*.—Butane-1 : 4-diol (10 g.) in pyridine (30 c.c.) was cooled to 0° and a solution of methanesulphonyl chloride (28 g.) in pyridine (50 c.c.) added slowly with stirring. After 2 hours the product was worked up in the usual way to give the *dimethanesulphonate* (22 g.), needles (from methanol–acetone), m. p. 116° (Found: C, 29·6; H, 5·7; S, 25·7. $C_6H_{14}O_6S_2$ requires C, 29·3; H, 5·7; S, 26·0%). The aqueous filtrates were acidified and extracted three times with light petroleum (b. p. 100—120°). The dried (K_2CO_3) extracts were carefully fractionated, but no tetrahydrofuran could be detected.

The dimethanesulphonate (17 g.) was boiled under reflux with 16% aqueous potassium hydroxide (125 c.c.), a homogeneous solution being formed after 15 minutes. Direct distillation gave a low-boiling fraction, b. p. 63—95°, which was dried (K_2CO_3) and redistilled to give tetrahydrofuran (2·9 g., 58%), b. p. 64·5—65·5°, n_D^{23} 1·4085.

trans-2-*Chloromethyl*cyclo*hexylmethanol*.—The *trans*-diol (10 g.) was heated at 80—90° with fuming hydrochloric acid (10 c.c.; *d* 1·19) for 19 hours (sealed tube). The upper layer was separated, washed with water and sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled to give crude trans-2-*chloromethyl*cyclo*hexylmethanol* (5·2 g.), b. p. 79—83°/0·3 mm., n_D^{16} 1·4878—1·4942. A fraction, b. p. 82—83°/0·3 mm., n_D^{16} 1·4918, was analysed (Found: C, 60·3; H, 9·5; Cl, 21·2. $C_8H_{15}OCl$ requires C, 59·1; H, 9·3; Cl, 21·8%). Hydrogen chloride and crude oxide (0·65 g.) were found in the liquid-air trap after the distillation. When the monochloride was heated to about 200° it lost hydrogen chloride, and the residue had a strong odour of the oxide. Treatment of the crude monochloride with *p*-nitrobenzoyl chloride in pyridine gave a p-*nitrobenzoate* (60%) which from methanol formed fine needles, m. p. 61—62°, by slow crystallisation, or a microcrystalline powder, m. p. 64—65°, by rapid crystallisation. The two forms were interconvertible, and mixtures showed intermediate m. p.s (Found: C, 57·8; H, 5·9; N, 4·5. $C_{15}H_{18}O_4NCl$ requires C, 57·8; H, 5·8; N, 4·5%).

Attempted Preparation of the trans-*Monotoluene*-p-*sulphonate*.—(i) To a solution of the *trans*-diol (2 g.) in pyridine (20 c.c.) at 0° a solution of toluene-*p*-sulphonyl chloride (2·65 g.) in chloroform (20 c.c.) was added dropwise, with stirring, during 4 hours. Pyridine and chloroform were removed under reduced pressure below 35°, and the residue was dissolved in chloroform, washed successively with dilute sulphuric acid and sodium hydrogen carbonate solution, and dried (Na_2SO_4). Removal of solvent then gave a viscous yellow oil (2·15 g.), n_D^{19} 1·5185, having an odour of the oxide. This was dissolved in methanol (2 c.c.), cooled to 0° and filtered from a small quantity of *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 108°. Removal of solvent from the filtrate, followed by methanesulphonation in pyridine, gave an oil from which a small quantity of *trans*-dimethanesulphonate, m. p. and mixed m. p. 92°, separated on addition of methanol and cooling at 0°. Similar results were obtained when the toluene-*p*-sulphonation was carried out in chloroform–pyridine (1 : 1) solution during 4 days.

(ii) *trans*-2-Chloromethyl*cyclo*hexylmethanol (4 g.) in dry benzene (50 c.c.) was heated

under reflux with silver toluene-*p*-sulphonate (12 g.) for 16 hours. Filtration and removal of solvent gave an oil with a strong odour of the oxide; the latter was removed in a high vacuum at room temperature to leave a residue (0·3 g.) of viscous oil which failed to give any crystalline derivatives. The material collected in the liquid-air trap was dried (K_2CO_3) and distilled to give the *trans*-oxide (0·8 g.), b. p. 74°/20 mm., n_D^{25} 1·4647.

trans-1 : 2-*Bisbromomethyl*cyclo*hexane*.—Dry hydrogen bromide was passed into *trans*-octahydro*iso*benzofuran (50 g.) at 80—90°. Absorption was rapid at first, but became slower when, after 1½ hours, a lower aqueous layer began to separate. After a further 3½ hours the reaction was discontinued and the brown oil was dissolved in chloroform, washed with water and sodium hydrogen carbonate solution, and dried (Na_2SO_4). Removal of solvent, followed by distillation, gave trans-1 : 2-*bisbromomethyl*cyclo*hexane* (68 g., 63%), b. p. 102°/0·5 mm., n_D^{20} 1·5390 (Found : C, 35·6; H, 5·5; Br, 59·25. $C_8H_{14}Br_2$ requires C, 35·6; H, 5·2; Br, 59·2%).

Reaction of the dibromide (1 g.) with sodium iodide (3·5 g.) in boiling acetone for 1½ hours gave a precipitate (0·62 g., 81%) of sodium bromide. Evaporation of the filtered solution and addition of water to the residue gave a solid, which on recrystallisation from methanol furnished *trans*-1 : 2-bisiodomethyl*cyclo*hexane (0·45 g.), m. p. and mixed m. p. 39—40°.

trans-1 : 2-*Bisacetoxymethyl*cyclo*hexane*.—The *trans*-dibromide (47 g.), acetic acid (150 c.c.), fused potassium acetate (60 g.), and acetic anhydride (10 c.c.) were boiled under reflux overnight. The isolated product still contained bromine and it was therefore refluxed for 2 hours with silver acetate (15 g.) in acetic acid (150 c.c.), and worked up to yield the trans-*diacetate* (16·3 g.), b. p. 104—107°/0·5 mm., n_D^{23} 1·4580 (Found : C, 62·5; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·15; H, 8·8%). This (7 g.) was stored for 48 hours in methanol (60 c.c.) containing sodium methoxide (0·2 g.). The solution was then neutralised with carbon dioxide and evaporated to a viscous oil which was taken up in ether, dried (Na_2SO_4), evaporated, and distilled to give the *trans*-diol (3·55 g.), m. p. *ca.* 43°, raised to 57° by recrystallisation. Toluene-*p*-sulphonation gave the *trans*-ditoluene-*p*-sulphonate, m. p. and mixed m. p. 108°.

Toluene-p-*sulphonate of* trans-2-*Chloromethyl*cyclo*hexylmethanol*.—The ***trans***-oxide (5 g.), toluene-*p*-sulphonyl chloride (8·2 g.), and zinc chloride (5 mg.) were heated together for 3 hours at 100°. The dark, viscous product was dissolved in chloroform and washed with sodium hydrogen carbonate solution and with water. Evaporation of the dried (Na_2SO_4) solution gave a brown oil, having a strong odour of toluene-*p*-sulphonyl chloride. Treatment with charcoal in methanol and filtration of a solution in benzene through activated alumina eliminated acid chloride and some of the colouring matter to give crude trans-2-*chloromethyl*cyclo*hexyl-methyl toluene*-p-*sulphonate* (7·1 g.) as a brown oil, n_D^{24} 1·5228 (Found : S, 9·15; Cl, 11·9. $C_{15}H_{21}O_3SCl$ requires S, 10·1; Cl, 11·2%).

When a solution of this product (5·8 g.) with sodium iodide (20 g.) in acetone (100 c.c.) was boiled under reflux for 48 hours, a mixture of sodium toluene-*p*-sulphonate and sodium chloride (3·1 g., 69%) was precipitated. Evaporation of the filtered solution, and extraction of the residue with chloroform, gave an oil which when dissolved in methanol and cooled to 0° deposited the *trans*-di-iodide (0·5 g.), m. p. and mixed m. p. 39—40°.

trans-2-*Chloromethyl*cyclo*hexylmethyl Acetate*.—The *trans*-oxide (10 g.) and acetyl chloride (10 g.) were heated at 100° for 3 hours. Water was added, and the ester was extracted with chloroform, washed with sodium hydrogen carbonate solution and with water, dried (Na_2SO_4), freed from solvent, and distilled to give trans-2-*chloromethyl*cyclo*hexylmethyl acetate* (13·6 g.), as a colourless oil, b. p. 87—89°/0·2 mm., n_D^{23} 1·4731 (Found : C, 58·6; H, 8·4; Cl, 17·45. $C_{10}H_{17}O_2Cl$ requires C, 58·7; H, 8·4; Cl, 17·3%). This ester (4 g.) was dissolved in 1% hydrogen chloride in methanol (100 c.c.). After 48 hours at room temperature the acid was neutralised with solid sodium hydrogen carbonate, and methanol distilled from the filtered solution. The residue was extracted with ether, and the ethereal extract distilled to give *trans*-2-chloromethyl*cyclo*hexylmethanol (1·8 g.), b. p. 78—82°/0·25 mm., n_D^{20} 1·4883—1·4940. The drift in refractive index was possibly due to the presence of a little unchanged acetate, but the product readily gave the *p*-nitrobenzoate, identical with that prepared previously, m. p. and mixed m. p. 61—62° or 64—65°.

2-*Bromomethyl*cyclo*hexylmethyl Acetate*.—(i) The *cis*-oxide (5·4 g.) was mixed with acetyl bromide (5·7 g.); a vigorous reaction ensued and external cooling was necessary. When the reaction subsided the mixture was heated at 100° for 30 minutes and then worked up as for the chloro-compound, to give cis-2-*bromomethyl*cyclo*hexylmethyl acetate* as a pale yellow oil (8·8 g.), b. p. 84—85°/0·15 mm., n_D^{18} 1·4967 (Found : C, 48·5; H, 7·0; Br, 32·8. $C_{10}H_{17}O_2Br$ requires C, 48·2; H, 6·9; Br, 32·1%). Deacetylation of this material (0·8 g.) as described for the chloro-compound gave the crude monobromide (0·6 g.), which with *p*-nitrobenzoyl chloride

in pyridine gave cis-2-*bromomethyl*cyclo*hexylmethyl* p-*nitrobenzoate*, needles (from ethanol), m. p. 79° (Found : C, 50·8; H, 5·3; N, 3·9. $C_{15}H_{18}O_4NBr$ requires C, 50·6; H, 5·1; N, 3·9%).

(ii) The *trans*-oxide (4·05 g.) and acetyl bromide (4·3 g.) similarly gave trans-2-*bromomethyl*-cyclo*hexylmethyl acetate* (6·7 g.), b. p. 80—83°/0·2 mm., n_D^{15} 1·4938 (Found : C, 48·2; H, 6·8; Br, 32·9%). Deacetylation and *p*-nitrobenzoylation gave trans-2-*bromomethyl*cyclo*hexylmethyl* p-*nitrobenzoate* as powdery crystals (from methanol), m. p. 80—81° (Found : C, 50·7; H, 5·1; N, 3·9%). The m. p. was depressed to 63° on admixture with the *cis*-isomer of m. p. 79°.

Reaction of Octahydroisobenzofuran with p-*Nitrobenzoyl Bromide.*—(i) The *cis*-oxide (0·27 g.), *p*-nitrobenzoyl bromide (0·52 g.), and a trace of zinc chloride were heated at 100° for 10 minutes. The product was dissolved in chloroform and washed with aqueous sodium hydrogen carbonate. The dried (Na_2SO_4) solution was evaporated to give a solid (0·6 g.), m. p. 76—78°, which by one recrystallisation from methanol yielded the *cis*-bromide *p*-nitrobenzoate, m. p. and mixed m. p. 79°.

(ii) The *trans*-oxide (0·25 g.) reacted similarly with *p*-nitrobenzoyl bromide (0·47 g.) and a trace of zinc chloride to give the *trans*-bromide *p*-nitrobenzoate (0·35 g.), m. p. and mixed m. p. 80—81°.

trans-2-*Iodomethyl*cyclo*hexylmethyl* p-*Nitrobenzoate.*—*trans*-2-Bromomethyl*cyclo*hexylmethyl acetate (11·5 g.) and sodium iodide (20 g.) in acetone (100 c.c.) were boiled under reflux for 1 hour. Sodium bromide (4·38 g., 95%) was filtered off, and the acetone distilled from the filtrate. The residue was extracted with chloroform, and the extract was washed with sodium thiosulphate solution to remove free iodine, and dried (Na_2SO_4). Removal of solvent gave an oil which distilled (some decomp.) to give an impure acetate–iodide (11·1 g.), b. p. 108—113°/0·5 mm., n_D^{12} 1·5171—1·5230. A fraction, b. p. 112°/0·5 mm., n_D^{12} 1·5220, was analysed (Found : I, 35·5. Calc. for $C_{10}H_{17}O_2I$: I, 42·9%). Deacetylation with methanolic hydrogen chloride, followed by *p*-nitrobenzoylation, gave trans-2-*iodomethyl*cyclo*hexylmethyl* p-*nitrobenzoate*, needles (from methanol), m. p. 55—56° (Found : C, 44·8; H, 4·7; N, 3·5. $C_{15}H_{18}O_4NI$ requires C, 44·7; H, 4·5; N, 3·5%).

Reduction of Methyl Phenylcarbamate.—The urethane (5 g.) in dry ether (20 c.c.) was added to a solution of lithium aluminium hydride (1·8 g.) in dry ether (100 c.c.). When the reaction subsided the solution was boiled under reflux for 2 hours. Water was then added, with sufficient sodium hydroxide to redissolve the precipitate, and the ethereal layer was removed, dried (K_2CO_3), and evaporated; distillation of the residue gave *N*-methylaniline (4·1 g.), b. p. 193—195° (acetyl derivative, m. p. 101°; toluene-*p*-sulphonyl derivative, m. p. 94—95°).

Reduction of the (−)-*Menthylurethane of* trans-1 : 2-*Bishydroxymethyl*cyclo*hexane.*—The more soluble fractions from the original resolution were used. The urethane (10 g.) and lithium aluminium hydride (1·5 g.) in dry ether (130 c.c.) were boiled under reflux for 3 hours. After the addition of water and sodium hydroxide the solution was steam-distilled to remove ether and amine; the latter was recovered by ether-extraction of the distillate and on distillation furnished *N*-(−)-menthylmethylamine (4·75 g.), b. p. 95—96°/13 mm., n_D^{21} 1·4569, $[\alpha]_D^{20}$ −68·9° (*c*, 2 in $CHCl_3$). Read and Hendry (*Ber.*, 1938, **71**, 2544) give b. p. 87°/12 mm., n_D^{17} 1·4587, $[\alpha]_D^{17}$ −69·2°. The toluene-*p*-sulphonyl derivative had m. p. 60—61°, $[\alpha]_D^{20}$ −36·8° (*c*, 2 in $CHCl_3$). Read and Hendry (*loc. cit.*) give m. p. 61°, $[\alpha]_D^{17}$ −37·5°.

The alkaline residue from the steam-distillation was continuously extracted with ether and gave the *trans*-diol (2·3 g.), b. p. 130—131°/0·5 mm., m. p. 55—56°, $[\alpha]_D$ −5·0° (*c*, 7 in EtOH); this was not optically pure [cf. the (+)-*trans*-diol, above] because the bismenthylurethane used was not a pure diastereoisomer. The toluene-*p*-sulphonate had m. p. 108°, not depressed by the (±)-derivative.

Reduction of the (−)-*Menthylurethane of* (−)-*Menthol.*—The urethane (Read and Roebuck, *loc. cit.*) (3·45 g.) and lithium aluminium hydride (0·6 g.) in dry ether (60 c.c.) were boiled under reflux overnight. Water and excess of sulphuric acid were added, and the ethereal layer was removed. The aqueous portion was extracted with ether, and the combined ethereal solutions on evaporation gave a residue which on sublimation at 100° (bath)/25 mm. gave (−)-menthol (0·15 g.), m. p. 40—41°, $[\alpha]_D^{20}$ −50·1° (*c*, 3 in EtOH). The involatile residue from the sublimation (2·4 g.), m. p. 107—109°, was unchanged urethane.

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80. *Alicyclic Glycols. Part IX.** 1 : 3-*Bishydroxymethyl*cyclohexane.

By G. A. Haggis and L. N. Owen.

The *cis*- and the *trans*-form of this diol (I) have been synthesised by reduction of the corresponding stereoisomers of hexahydro*iso*phthalic ester with lithium aluminium hydride, and the *trans*-diol has been resolved. Melting points of all derivatives of the *cis*-diol are higher than those of the corresponding *trans*-compounds. The intramolecular anhydro-compound, 3-oxa*bicyclo*[3 : 3 : 1]nonane (III) has been obtained from the *cis*-diol by hydrolysis of the dimethanesulphonate with aqueous alkali, and by reaction of the monotoluene-*p*-sulphonate with 2 : 6-lutidine, but ring-closure does not occur so readily as with the 1 : 2-isomer (Part VIII [•]). Fission of the tetrahydropyran ring in (III) has been effected with hydrogen bromide, acetyl chloride, acetyl bromide, and *p*-nitrobenzoyl bromide.

In the preceding paper it was shown that reduction of a *cis*- or a *trans*-hexahydrophthalic ester with lithium aluminium hydride occurred without epimerisation and gave the corresponding stereoisomer of 1 : 2-bishydroxymethyl*cyclo*hexane. Since the configurations of the hexahydro*iso*phthalic acids have been rigorously established, by anhydride-formation from the *cis*-acid (Baeyer and Villiger, *Annalen*, 1893, **276**, 261; Goodwin and Perkin, *J.*, 1905, **87**, 841) and by resolution of the *trans*-isomer (Böeseken and Peek, *Rec. Trav. chim.*, 1925, **44**, 845), both stereoisomers of the hitherto unknown 1 : 3-bishydroxymethyl*cyclo*hexane (I) should be readily obtainable by the same prodecure.

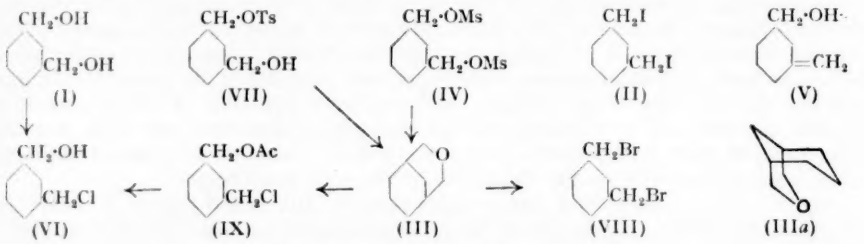
Over a freshly-prepared W-6 Raney nickel catalyst (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 695) hydrogenation of diethyl *iso*phthalate proceeded smoothly at 100°/100 atm. with only slight hydrogenolysis, and gave a good yield of the hexahydro-ester (with a catalyst prepared only two days before use a temperature of 150—200° was required, and considerable hydrogenolysis occurred). The hexahydro-ester was hydrolysed, and the *cis*-acid, which was the main product, was isolated as the insoluble calcium salt (Baeyer and Villiger, *loc. cit.*; Goodwin and Perkin, *loc. cit.*). The *trans*-isomer was obtained by partial isomerisation of the *cis*-acid with hydrochloric acid at 180° (Goodwin and Perkin, *loc. cit.*); unchanged *cis*-acid was removed as calcium salt and the *trans*-acid isolated from the residue. The acids were esterified and then individually reduced with lithium aluminium hydride to give *cis*-1 : 3-bishydroxymethyl*cyclo*hexane, m. p. 55°, and the liquid *trans*-isomer. The latter was resolved through the bis-(−)-menthylurethane, but owing to the unfavourable physical properties of this derivative the separation was more difficult than with the 1 : 2-isomer, and the (−)-*trans*-diol so obtained, $[\alpha]_D^{26}$ −9·6°, may not have been optically pure; its isolation, however, provides independent proof of the configuration.

The diols were characterised by the preparation of several derivatives, and it is noteworthy that in every case the *cis*-compound has the higher melting point. This inversion of the usual order occurs also with the derivatives of *cyclo*hexane-1 : 3-diol (Clarke and Owen, *J.*, 1950, 2103), and may be attributed to the different spatial arrangement of the bonds joining 1 : 3-substituents (compared with 1 : 2- and 1 : 4-) to the ring. Thus, with the more stable chair conformation it is the *trans*-1 : 3-compound in which the groups are attached in a way (one " equatorial " bond, one " polar ") similar to that in the *cis*-1 : 2- and *cis*-1 : 4-compounds, and *vice versa*. These considerations, which apply also to the dimethyl*cyclo*hexanes and methyl*cyclo*hexylmethanols, are discussed more fully in Part XI (*J.*, 1953, 408). Another interesting difference in behaviour was observed in the relative reactivities of the ditoluene-*p*-sulphonates towards sodium iodide in acetone; unlike the 1 : 2-compounds, the *cis*-1 : 3-derivative reacted more rapidly than the *trans*-isomer, and the solid *cis*-di-iodide (II) so formed was more stable than the liquid *trans*-di-iodide.

Steric considerations show that the *cis*-diol should be capable of forming an intramole-

* Part VIII, preceding paper.

cular ether, 3-oxa*bicyclo*[3 : 3 : 1]nonane (III), which, amongst other possibilities, could have the strainless " double-chair " structure (III*a*) (a similar conformation may apply to the anhydride of *cis*-hexahydro*iso*phthalic acid); no such product would be expected from the *trans*-diol. The methods which had been successful in the preparation of octahydro*iso*benzofuran from 1 : 2-bishydroxymethyl*cyclo*hexane (Part VIII) were therefore applied to *cis*-(I) and its derivatives. Hydrolysis of the dimethanesulphonate (IV) with aqueous alkali gave the oxide (III) in 30% yield, accompanied by a small amount of unsaturated material, the main product being the *cis*-diol; this contrasts with the behaviour of the 1 : 2-isomer, which gave no diol on hydrolysis. In a comparative experiment the *trans*-form of (IV) gave no cyclic oxide; the main product was the *trans*-diol, but an unsaturated product was also obtained, which probably contained 3-methylene*cyclo*hexylmethanol (V), characterised as the 3 : 5-dinitrobenzoate. Dehydration of the *cis*-diol with sulphuric acid in acetone gave the oxide in very small yield, and under more vigorous conditions, such as alumina at 200—250°, or hot 50% sulphuric acid, only unsaturated material was obtained. With fuming hydrochloric acid the diol gave a mixture of mono- and di-chlorides, with much polymer; the monochloride (VI) was characterised as the *p*-nitrobenzoate.



(Ms = $CH_3 \cdot SO_2 \cdot$; Ts = p-$C_6H_4Me \cdot SO_2 \cdot$)

Reynolds and Kenyon (*J. Amer. Chem. Soc.*, 1950, **72**, 1593; U.S.P. 2,544,899) described a method for the preparation of tetrahydro-furan and -pyran systems which involves treatment of the appropriate diol, in boiling pyridine or 2 : 6-lutidine, with 1 mol. of a sulphonyl chloride. Treatment of *cis*-(I) under these conditions with benzenesulphonyl chloride and 2 : 6-lutidine resulted only in the formation of a mixture of mono- and di-chlorides, the presence of (VI) being confirmed by conversion into the *p*-nitrobenzoate mentioned above. Production of a chloride, rather than a sulphonyl ester, from an alcohol and a sulphonyl chloride in pyridine is known to take place at high temperatures (Tipson, *J. Org. Chem.*, 1944, **9**, 235), or even at low temperatures with highly reactive compounds (Miles and Owen, *J.*, 1950, 2938), and this side reaction was encountered by Reynolds and Kenyon in some of their experiments.

Reynolds and Kenyon (*loc. cit.*) described a variation of their method, in which cyclisation was effected by reaction of a monosulphonate of a diol with the organic base. Reaction of *cis*-(I) with 1 mol. of toluene-*p*-sulphonyl chloride in pyridine gave a crude monotoluene-*p*-sulphonate (VII), which with boiling 2 : 6-lutidine gave the oxide (III) in 36% yield; this route, however, gave variable results, probably owing to the critical conditions of monotoluene-*p*-sulphonation. The best method, therefore, is the hydrolysis of the *cis*-dimethanesulphonate, but from the relative yields of cyclic ether in the 1 : 2- and the 1 : 3-series it is clear that the six- is formed much less readily than the five-membered oxide ring; although a cyclic oxide was prepared from 3-hydroxymethyl*cyclo*hexanol (Clarke and Owen, *J.*, 1950, 2108) no analogous product was obtained from 4-hydroxymethyl-*cyclo*hexanol (Owen and Robins, *J.*, 1949, 326).

3-Oxa*bicyclo*[3 : 3 : 1]nonane was a volatile, waxy solid, m. p. 113—115°, very soluble in organic solvents, and could be satisfactorily purified only by sublimation. With hydroferricyanic acid it formed a complex which was less stable than that from octahydro*iso*benzofuran.

Although a tetrahydropyran ring can usually be cleaved by most of the reagents which

attack tetrahydrofuran systems (cf. Jones and Taylor, *Quart. Reviews*, **1950**, **4**, 195), more drastic conditions are sometimes required and the yields are often poorer. This distinction is well illustrated in the reactions of (III). Unlike octahydro*iso*benzofuran (cf. Part VIII) it did not readily react with hydrogen bromide at 70—80°, but with hydrogen bromide in acetic acid at 100° it gave *cis*-1 : 3-bisbromomethyl*cyclo*hexane (VIII), the configuration of which was proved by reaction with potassium acetate and deacetylation of the resulting diacetate to the *cis*-diol. Also in contrast to octahydro*iso*benzofuran, it failed to react with acetyl chloride or acetyl bromide in the absence of a catalyst, though in the presence of zinc chloride it readily gave *cis*-3-chloromethyl- (IX) and *cis*-3-bromomethyl-*cyclo*hexylmethyl acetate. Deacetylation of (IX) gave the chlorohydrin (VI), characterised as the *p*-nitrobenzoate, identical with that prepared from the mixtures of mono- and di-chlorides. Similarly, deacetylation and *p*-nitrobenzoylation of the bromo-compound gave *cis*-3-bromomethyl*cyclo*hexylmethyl *p*-nitrobenzoate, which was also obtained by direct reaction of the oxide with *p*-nitrobenzoyl bromide in the presence of zinc chloride.

Experimental

Dimethyl cis-*Hexahydro*iso*phthalate*.—Diethyl *iso*phthalate (195 g.) in ethanol (300 c.c.) was hydrogenated over freshly-prepared W-6 Raney nickel (Adkins and Billica, *loc. cit.*) (40 g.) at 100°/100 atm. When uptake was complete the catalyst was filtered off and the filtrate distilled to give the crude hexahydro-ester (170 g.), b. p. 85—125° (mainly 120—125°)/1 mm., n_D^{20} 1·4568. This was hydrolysed with boiling ethanolic alkali, water added, and the ethanol distilled off. The residual aqueous solution was acidified, and then made alkaline with ammonia and treated with excess of calcium chloride solution. The precipitated calcium salt was filtered off, and the acid regenerated from it by concentrated hydrochloric acid. Crystallisation from hot water gave the *cis*-acid (100 g.), m. p. 161—162° (Goodwin and Perkin, *loc. cit.*, gave m. p. 161—163°), which was converted into the dimethyl ester (100 g.), b. p. 94—96°/0·2 mm., n_D^{20} 1·4580, by methanol and sulphuric acid.

Dimethyl trans-*Hexahydro*iso*phthalate*.—The *cis*-acid (40 g.) and concentrated hydrochloric acid (60 c.c.) were heated together for 16 hours at 180° (sealed tube). Excess of aqueous ammonia was then added, and the *cis*-acid precipitated as the calcium salt as described above. This was filtered off, and the filtrate acidified and continuously extracted with ether. The acid thus obtained was dissolved in the minimum amount of aqueous ammonia (*d* 0·88) and treated with calcium chloride to precipitate a further small quantity of *cis*-acid. The filtered solution was acidified, and the precipitated acid crystallised from hot water to give the pure *trans*-acid (8·6 g.), m. p. 147—148° (Goodwin and Perkin, *loc cit.*, gave m. p. 148°). The acid was esterified in the usual way to give the *trans*-dimethyl ester (7·8 g.), b. p. 83—85°/0·1 mm., n_D^{18} 1·4592.

1 : 3-*Bishydroxymethyl*cyclo*hexane*.—(i) The *cis*-dimethyl ester (50 g.) in dry ether (50 c.c.) was added dropwise to a stirred, cooled solution of lithium aluminium hydride (11·5 g.) in dry ether (500 c.c.). After 1 hour water and dilute sulphuric acid were added and the diol was isolated by continuous extraction with ether. Removal of ether from the dried (K_2CO_3) extracts gave cis-1 : 3-*bishydroxymethyl*cyclo*hexane* (35 g., 97%) as a viscous oil, which slowly crystallised and had m. p. 50—53°, raised to 54—55° by recrystallisation from dry ether (Found : C, 66·2; H, 11·3. $C_8H_{16}O_2$ requires C, 66·6; H, 11·2%).

(ii) Similarly, reduction of the *trans*-dimethyl ester (14·1 g.) with lithium aluminium hydride (3·5 g.) gave trans-1 : 3-*bishydroxymethyl*cyclo*hexane* (9·2 g., 91%), b. p. 112—114°/0·1 mm., n_D^{24} 1·4941 (Found : C, 66·5; H, 11·0%).

Derivatives of the cis-*Diol*.—Treatment of the *cis*-diol (0·5 g.) with toluene-*p*-sulphonyl chloride (1·45 g.) in pyridine (5 c.c.) for 20 hours at 0°, followed by precipitation with ice, gave the *ditoluene*-p-*sulphonate* (1 g., 64%), which crystallised from methanol in plates, m. p. 99—100° (Found : C, 58·3; H, 6·5; S, 14·1. $C_{22}H_{28}O_6S_2$ requires C, 58·4; H, 6·2; S, 14·2%). A similar procedure gave the *dimethanesulphonate* (75%), needles, m. p. 74—75° (Found : C, 40·1; H, 6·9; S, 21·3. $C_{10}H_{20}O_6S_2$ requires C, 40·0; H, 6·7; S, 21·35%), from methanol, and the *di*-p-*nitrobenzoate*, a microcrystalline powder (95%), m. p. 151—152° (Found : C, 59·3; H, 5·1; N, 6·1. $C_{22}H_{22}O_8N_2$ requires C, 59·7; H, 5·0; N, 6·3%), from methanol–acetone.

The *cis*-diol (0·3 g.) with phenyl *iso*cyanate (0·6 g.) at 100° (1 hr.) gave the *bisphenylurethane* (0·6 g., 76%), m. p. 128—129° [from benzene–light petroleum (b. p. 60—80°)] (Found : C, 68·9; H, 6·75; N, 7·3. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·85; N, 7·3%).

Derivatives of the trans-*Diol*.—Under conditions identical with those described above,

including crystallisation solvents, there were obtained : the *ditoluene*-p-*sulphonate* (51%), plates, m. p. 86—87° (Found : C, 58·4; H, 6·5; S, 13·7%); the *dimethanesulphonate* (48%), needles, m. p. 64—65° (Found : C, 39·9; H, 6·9; S, 20·6%); the *di*-p-*nitrobenzoate* (67%), m. p. 122—123° (Found : C, 59·7; H, 5·2; N, 6·2%); and the *bisphenylurethane* (70%), m. p. 107—108° (Found : C, 69·3; H, 6·9; N, 7·4%).

Resolution of (±)-trans-1 : 3-*Bishydroxymethyl*cyclo*hexane*.—The *trans*-diol (5 g.) and (−)-menthyl *iso*cyanate (13·5 g.) in dry benzene (15 c.c.) were heated on the steam-bath overnight. Benzene was distilled off, and the syrupy residue dissolved in light petroleum (b. p. 40—60°). On cooling to 0° the urethane separated as a gelatinous mass, which was filtered off, pressed to remove solvent, and washed with light petroleum (b. p. 40—60°). The material so obtained was dried *in vacuo* to an amorphous powder (11 g.), m. p. 68—72°, $[\alpha]_D^{22}$ −59·1° (*c*, 2 in C_6H_6). Six further similar purifications gave a (−)-*menthylurethane* (2·05 g.), m. p. 92—95°, $[\alpha]_D^{22}$ −57·9° (Found : C, 71·5; H, 10·9; N, 5·3. $C_{30}H_{54}O_4N_2$ requires C, 71·1; H, 10·7; N, 5·5%). No solvent was found from which the urethane could be satisfactorily crystallised (cf. *inter al.*, Morgan and Pettet, *J.*, 1931, 1124; Fieser and Creech, *J. Amer. Chem. Soc.*, 1939, **61**, 3502).

The urethane (1·7 g.) was boiled under reflux for 48 hours in ethanol (30 c.c.) containing potassium hydroxide (2 g.). The solution was then steam-distilled to remove ethanol and (−)-menthylamine, and the diol was isolated by continuous extraction of the residual aqueous solution with ether. Distillation gave the (−)-trans-*diol* (0·36 g.) as a viscous oil, b. p. 113—115°/0·1 mm., n_D^{20} 1·4911, $[\alpha]_D^{20}$ −9·6° (*c*, 5 in EtOH) (Found : C, 67·0; H, 11·3%). The *ditoluene*-p-*sulphonate* had m. p. 73—74°, $[\alpha]_D^{20}$ −13° (*c*, 0·7 in C_6H_6) (Found : C, 58·05; H, 6·3%).

1 : 3-*Bisiodomethyl*cyclo*hexane*.—(i) The *cis*-ditoluene-*p*-sulphonate (1·5 g.) was boiled under reflux for 1½ hours with sodium iodide (4 g.) in acetone (50 c.c.). Sodium toluene-*p*-sulphonate (1·15 g., 89%) was filtered off, and acetone distilled from the filtrate. Water and chloroform were added, and the product, isolated from the chloroform solution, on distillation gave the cis-*di-iodide* (0·8 g.), m. p. 28°, b. p. 98—100°/3 × 10^{-4} mm., n_D^{19} 1·6055 (Found : C, 26·8; H, 3·8; I, 68·5. $C_8H_{14}I_2$ requires C, 26·4; H, 3·9; I, 69·7%).

(ii) The *trans*-ditoluene-*p*-sulphonate (1·9 g.) reacted much more slowly under similar conditions and gave an impure *trans*-di-iodide (1·2 g.) (Found : I, 63·5%).

Reaction of the cis-*Diol with Hydrochloric Acid*.—The *cis*-diol (10 g.) and fuming hydrochloric acid (10 c.c.) were heated at 80—90° for 4 hours (sealed tube). The product was extracted with ether, washed with aqueous sodium hydrogen carbonate and with water, and dried (Na_2SO_4). Distillation gave a main fraction (1·1 g.), b. p. 70—78°/0·03 mm., n_D^{18} 1·4916 (Found : Cl, 33·1. Calc. for $C_8H_{15}OCl$: Cl, 21·8. Calc. for $C_8H_{14}Cl_2$: Cl, 39·2%), and a large involatile residue. Treatment of the mixture of mono- and di-chlorides with *p*-nitrobenzoyl chloride in pyridine gave a small yield of cis-3-*chloromethyl*cyclo*hexylmethyl* p-*nitrobenzoate*, which crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 69° (Found : C, 57·7; H, 6·0; N, 4·4. $C_{15}H_{18}O_4NCl$ requires C, 57·8; H, 5·8; N, 4·5%).

3-*Oxa*bicyclo[3 : 3 : 1]*nonane*.—(i) A suspension of the *cis*-dimethanesulphonate (30 g.) in 15% aqueous potassium hydroxide (100 c.c.) was boiled under reflux for 3 hours. A solid sublimed into the condenser during the hydrolysis; this was washed out with ether, and the etheral solution dried (K_2CO_3) and evaporated. Sublimation of the residue at 110° (bath)/140 mm. gave 3-*oxa*bicyclo[3 : 3 : 1]*nonane* (3·1 g.), as a waxy solid with a camphoraceous odour, m. p. 105—110°, raised to 113—115° by resublimation (Found : C, 75·9; H, 11·3. $C_8H_{14}O$ requires C, 76·1; H, 11·2%). The small oily residue from the sublimation was unsaturated. The aqueous solution from the hydrolysis was steam-distilled to remove traces of volatile material and then continuously extracted with ether to give the *cis*-diol (10·5 g.), identified as the ditoluene-*p*-sulphonate, m. p. and mixed m. p. 99—100°.

In a comparative experiment, similar treatment of the *trans*-dimethanesulphonate (2·8 g.) gave no sublimate, but steam-distillation afforded a volatile oil, isolated by extraction with ether, which on distillation gave an unsaturated liquid (0·25 g.), b. p. 110—112°/20 mm., n_D^{25} 1·4798 (Found : C, 72·2; H, 10·8%); this probably contained 3-methylene*cyclo*hexylmethanol, since it gave a 3 : 5-*dinitrobenzoate*, crystallising from methanol in needles, m. p. 57° (Found : C, 55·9; H, 5·3. $C_{15}H_{16}O_6N_2$ requires C, 56·25; H, 5·0%). Ether-extraction of the non-volatile residue from the steam-distillation gave the *trans*-diol (0·5 g.), identified as the ditoluene-*p*-sulphonate, m. p. and mixed m. p. 86—87°.

(ii) To a solution of the *cis*-diol (4·5 g.) in chloroform–pyridine (1 : 1; 100 c.c.) kept at 0°, a solution of toluene-*p*-sulphonyl chloride (6·1 g.) in the same solvent (100 c.c.) was added dropwise during 4 hours, with vigorous stirring. The mixture was kept at 0° overnight and then concentrated under reduced pressure below 35°. The product was worked up into chloroform,

washed and dried in the usual way, and isolated as an oil. This was dissolved in methanol (*ca.* 10 c.c.), cooled to 0°, and filtered from a small quantity of ditoluene-*p*-sulphonate. Evaporation then gave the crude *cis*-monotoluene-*p*-sulphonate, probably contaminated with some unchanged diol (Found: S, 7·7. Calc. for $C_{15}H_{22}O_4S$: S, 10·7%). A solution of this product (3·9 g.) in 2 : 6-lutidine (7 c.c.) was boiled under reflux for an hour. The mixture, which had separated into two layers, was cooled and added to an excess of dilute sulphuric acid. Ether-extraction, followed by sublimation, gave 3-oxa*bicyclo*[3 : 3 : 1]nonane (0·6 g.), m. p. 113—114°. Repetition of this process on a larger scale gave a much smaller yield of the oxide.

(iii) The *cis*-diol (5 g.) in boiling 2 : 6-lutidine (15 g.) was treated with benzenesulphonyl chloride (6·2 g.), added dropwise during 15 minutes. After being heated for a further 15 minutes the solution was poured into excess of concentrated hydrochloric acid and extracted with ether. The dried (K_2CO_3) extracts were evaporated to a yellow oil, which on sublimation gave only a trace of oxide. Distillation of the residue yielded a mixture of mono- and di-chloride (2·6 g.), b. p. 148—151°/35 mm., n_D^{22} 1·4834 (Found: Cl, 28·1. Calc. for $C_8H_{15}OCl$: Cl, 21·8. Calc. for $C_8H_{14}Cl_2$: Cl, 39·2%), which gave *cis*-3-chloromethyl*cyclo*hexylmethyl *p*-nitrobenzoate, m. p. and mixed m. p. 69°.

This mixture (2 g.) was boiled for 16 hours with 10% aqueous potassium hydroxide (20 c.c.). The product, isolated by steam-distillation and ether-extraction, on sublimation gave the crystalline oxide (50 mg.) and left a residue which was unsaturated and contained chlorine.

Ring-fission of 3-*Oxa*bicyclo[3 : 3 : 1]*nonane*.—(i) *With hydrogen bromide*. The oxide (0·75 g.) and hydrogen bromide in acetic acid (20 c.c. of 50% solution) were heated at 100° for 4 hours (sealed tube). Hydrogen bromide and acetic acid were removed under reduced pressure and the residue was dissolved in chloroform, washed with aqueous sodium hydrogen carbonate and with water, and dried (Na_2SO_4). Distillation gave cis-1 : 3-*bisbromomethyl*cyclo*hexane* (1·33 g.), b. p. 93—96°/0·4 mm., n_D^{16} 1·5384 (Found: C, 35·8; H, 5·4; Br, 58·8. $C_8H_{14}Br_2$ requires C, 35·6; H, 5·2; Br, 59·2%).

This dibromide (1·2 g.) was boiled under reflux for 24 hours with potassium acetate (10 g.) in acetic acid (50 c.c.) containing acetic anhydride (1 c.c.). The bulk of the acetic acid was removed under reduced pressure, and water added to the residue. Extraction with ether gave cis-1 : 3-*bisacetoxymethyl*cyclo*hexane* (0·63 g.), b. p. 105—107°/0·5 mm., n_D^{15} 1·4598 (Found: C, 63·3; H, 8·9. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%), which on deacetylation by treatment of a portion (0·45 g.) with sodium (0·1 g.) dissolved in dry methanol (30 c.c.) for 24 hours at room temperature gave the *cis*-diol (0·3 g.), characterised as the ditoluene-*p*-sulphonate, m. p. and mixed m. p. 99—100°.

(ii) *With acetyl chloride*. The oxide (0·3 g.), acetyl chloride (0·25 g.), and zinc chloride (20 mg.) were heated under reflux on the steam-bath for 30 minutes, by which time boiling had ceased. The product was dissolved in chloroform, washed with sodium hydrogen carbonate solution and with water, and dried (Na_2SO_4). Distillation gave cis-3-*chloromethyl*cyclo*hexylmethyl acetate* (0·4 g.), b. p. 68—70°/0·3 mm., n_D^{22} 1·4711 (Found: C, 59·1; H, 8·4; Cl, 16·8. $C_{10}H_{17}O_2Cl$ requires C, 58·7; H, 8·35; Cl, 17·3%). Catalytic deacetylation with 1% hydrogen chloride in methanol, followed by *p*-nitrobenzoylation, gave the *p*-nitrobenzoate, m. p. and mixed m. p. 69°.

(iii) *With acetyl bromide*. The oxide (2 g.), acetyl bromide (2·5 g.), and zinc chloride (0·1 g.) reacted as above to give cis-3-*bromomethyl*cyclo*hexylmethyl acetate* (3·2 g.), b. p. 92—95°/0·4 mm., n_D^{22} 1·4890 (Found: C, 48·3; H, 7·0; Br, 32·7. $C_{10}H_{17}O_2Br$ requires C, 48·2; H, 6·9; Br, 32·1%). Catalytic deacetylation with 1% hydrogen chloride in methanol, followed by *p*-nitrobenzoylation, gave the cis-p-*nitrobenzoate*, needles [from light petroleum (b. p. 60—80°)], m. p. 79° (Found: C, 50·6; H, 5·1; N, 3·9. $C_{15}H_{18}O_4NBr$ requires C, 50·6; H, 5·1; N, 3·9%).

(iv) *With* p-*nitrobenzoyl bromide*. The oxide (0·15 g.), *p*-nitrobenzoyl bromide (0·4 g.), and zinc chloride (trace) were heated at 100° for 15 minutes. The product, isolated by chloroform extraction as in (ii), was a solid, which on crystallisation from light petroleum (b. p. 60—80°) gave *cis*-3-bromomethyl*cyclo*hexylmethyl *p*-nitrobenzoate (0·4 g.), m. p. and mixed m. p. 79°.

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81. *Alicyclic Glycols. Part X.** 1 : 4-*Bishydroxymethylcyclohexane.*

By G. A. Haggis and L. N. Owen.

The configurations of the stereoisomers of this diol have been confirmed by preparation of the *cis*-isomer by reduction of dimethyl *cis*-hexahydroterephthalate with lithium aluminium hydride. Some reactions of the methanesulphonates and toluene-*p*-sulphonates are described. Attempts to prepare an intramolecular anhydride, analogous to those obtained from the 1 : 2- and 1 : 3-isomers (Parts VIII and IX *) were unsuccessful. Alkaline hydrolysis of the *cis*- or *trans*-dimethanesulphonate, although resulting chiefly in substitution, also gives rise to some elimination, to yield 4-methylene*cyclo*hexylmethanol.

The 1 : 4-bishydroxymethyl*cyclo*hexanes (I) were first prepared by Malachowski, Wasowska, Jóźkiewcz, Adamiczka, and Zimmerman-Pasternak (*Ber.*, 1938, **71**, 759) by reduction of diethyl hexahydroterephthalate with sodium and alcohol. From either the *cis*- or the *trans*-hexahydro-ester they obtained a stereoisomeric mixture of diols, which were separated by fractional crystallisation of the dibenzoates and hydrolysis of these to give the *cis*- and the *trans*-diol, m. p. 43° and 67°, respectively. The configurations were related to those of the corresponding diamines, which in turn were rigorously correlated with those of the hexahydro-acids. The diol has also been obtained, again as a mixture of stereoisomers, by high-temperature hydrogenation of the hexahydro-ester over a chromite catalyst (U.S.P. 2,105,664).

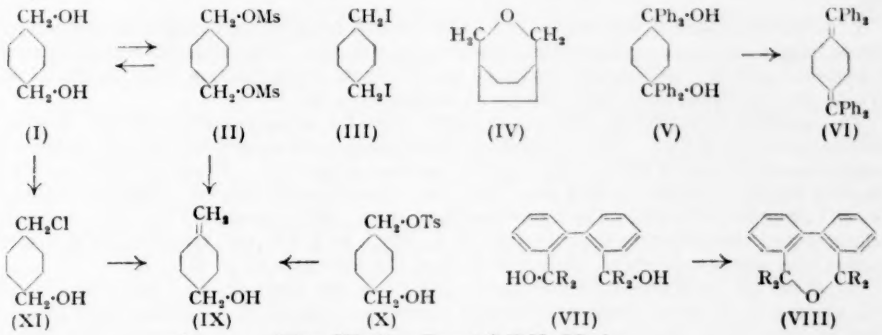
In the present work the diols were prepared by the method of Malachowski *et al.*, except that they were regenerated from the dibenzoates more conveniently, and in almost quantitative yield, by catalytic solvolysis with methanolic sodium methoxide, rather than by alkaline hydrolysis. The *cis*-isomer was also obtained by reduction of dimethyl *cis*-hexahydroterephthalate with lithium aluminium hydride. Since this method of reduction is known to occur with complete retention of configuration (see Parts VIII and IX, *J.*, 1953, 389, and *loc. cit.*), this provides independent proof of the configurations of the diols, because those of the hexahydroterephthalic acids are known with certainty (Mills and Keats, *J.*, 1935, 1373).

The diols were characterised by four derivatives from each, the melting points of the *trans*-compounds all being higher than those of their *cis*-isomers. The *trans*-diol also gave a solid diacetate. The dimethanesulphonates (II) reacted smoothly with sodium iodide in boiling acetone to give the corresponding *cis*- or *trans*-di-iodide (III), the latter being solid. The *trans*-ditoluene-*p*-sulphonate with lithium bromide in ethanol gave the *trans*-dibromide, m. p. 55°, previously prepared by Malachowski *et al.* from the diol and hydrobromic acid.

In Parts VIII and IX (*locc. cit.*) it was shown that intramolecular ethers are formed from both the *cis*- and the *trans*-1 : 2-bishydroxymethyl*cyclo*hexane, but only from the *cis*-1 : 3-isomer. Steric considerations make it clear that with the 1 : 4-compounds a cyclic oxide (IV) could only be derived from the *cis*-form, and it would necessarily be of the boat conformation (a similar structure must apply to the anhydride of *cis*-hexahydroterephthalic acid). Compounds containing seven-membered oxide rings are uncommon, and attempts to prepare them sometimes result in the formation of isomers containing smaller rings. Thus Franke and Kroupa (*Monatsh.*, 1936, **69**, 167) found that dehydration of hexane-1 : 6-diol with 50% sulphuric acid gave a mixture of 2-ethyltetrahydrofuran, 2-methyltetrahydropyran, and hexamethylene oxide, in which the first two predominated; pure hexamethylene oxide was later obtained as a by-product of the action of hydrobromic acid on hexane-1 : 6-diol (Müller and Vanc, *Ber.*, 1944, **77**, 669). Wittig and Pook (*Ber.*, 1937, **70**, 2485) found that dehydration of the *cis*- and the *trans*-tetraphenyl-substituted diol (V) with sulphuric acid in acetic acid gave the unsaturated hydrocarbon (VI), though in this case the tertiary nature of both hydroxyl groups probably favours the elimination. On the other hand, diols of the type (VII; R = H, Me, or Ph), in which olefin-formation is

* Part IX, preceding paper.

impossible, are readily dehydrated to the corresponding oxides (VIII) (Wittig and Petri, *Annalen*, 1933, **505**, 17; Bennett and Wain, *J.*, 1936, 1114; Hall and Turner, *J.*, 1951, 3072).



(Ms = $CH_3 \cdot SO_2$; Ts = p-$C_6H_4Me \cdot SO_2$·.)

In view of these facts, and of the results obtained with the 1 : 3-isomers (Part IX, *loc. cit.*), attention was concentrated on the hydrolysis of the mono- and di-esters of the diol, rather than on methods involving direct dehydration, and although cyclisation was likely to occur only in the *cis*-series, the *trans*-compounds were also studied for comparative purposes. Hydrolysis of the *cis*- or the *trans*-dimethanesulphonate (II) with aqueous potassium hydroxide gave the corresponding diol as the major product, but a small amount of a lower-boiling liquid was also formed. The latter, although having the correct composition for the expected cyclic oxide (IV), $C_8H_{14}O$, contained one double bond (quantitative hydrogenation), a hydroxyl group (3 : 5-dinitrobenzoate) and an exocyclic methylene group (evolution of formaldehyde on ozonolysis), and was therefore 4-methylene*cyclo*hexylmethanol (IX). Its formation is of interest because it arises from the unusual process of elimination from a primary methanesulphonate.

Monoesterification of the *cis*- and the *trans*-diol was carried out under mild conditions by slow addition of 1 mol. of toluene-*p*-sulphonyl chloride to the diol in chloroform–pyridine at 0°. The resulting liquid monotoluene-*p*-sulphonates were characterised as the solid *cis*-*p*-nitrobenzoate–toluene-*p*-sulphonate and *trans*-methanesulphonate–toluene-*p*-sulphonate. Treatment of the *cis*-monotoluene-*p*-sulphonate (X) with boiling 2 : 6-lutidine, according to the method used by Reynolds and Kenyon (*J. Amer. Chem. Soc.*, 1950, **72**, 1593; U.S.P. 2,544,899) for the formation of tetrahydro-furan and -pyran rings, gave only the unsaturated alcohol (IX), identified as the 3 : 5-dinitrobenzoate. Hydrolysis of the *trans*-monotoluene-*p*-sulphonate with aqueous sodium hydroxide gave the *trans*-diol and a small amount of unsaturated material.

When heated with a limited amount of fuming hydrochloric acid, the *trans*-diol gave 4-chloromethyl*cyclo*hexylmethanol (XI), characterised as the crystalline *p*-nitrobenzoate; treatment of this monochloride with aqueous sodium hydroxide gave the *trans*-diol and unsaturated material, probably mainly (IX).

The formation of (IX) in our attempts to form a cyclic oxide is of interest in view of the results of Malachowski *et al.* (*loc. cit.*): in the hope of obtaining a cyclic imine analogous to (IV) they heated the hydrochloride of the diamine corresponding to *cis*-(I), but obtained only 4-methylene*cyclo*hexylmethylamine, the amino-analogue of (IX).

Experimental

Diethyl Hexahydroterephthalate.—Diethyl terephthalate (49 g.) in ethanol (400 c.c.) was hydrogenated over Raney nickel (5 g.) at 200°/100 atm. Distillation gave the crude hexahydro-ester (47 g.), b. p. 75—115° (mainly 105—115°)/0·4 mm., n_D^{18} 1·4615.

Dimethyl cis-*Hexahydroterephthalate.*—The crude hexahydro-ester was hydrolysed by boiling aqueous-alcoholic sodium hydroxide, and the solution was acidified and steam-distilled to remove hydrogenolysis products; the hexahydro-acid was then isolated from the aqueous solution by continuous ether-extraction. The *cis*-acid, m. p. 160—161° (recorded m. p.s vary

from 161—162° to 170—171°), was separated from a small quantity of *trans*-acid by crystallisation from chloroform (in which the latter is insoluble) and converted into the dimethyl ester, b. p. 110°/1 mm., n_D^{16} 1·4595, by methanol and sulphuric acid (cf. Baeyer, *Annalen*, 1888, **245**, 174).

1 : 4-*Bishydroxymethyl*cyclo*hexane*.—(i) Crude diethyl hexahydroterephthalate was reduced with sodium in alcohol according to Malachowski *et al.* (*loc. cit.*). The crude diol was benzoylated in pyridine, and the dibenzoates separated by fractional crystallisation from methanol and acetone into the *trans*-, m. p. 125°, and the *cis*-isomer, m. p. 84°.

The *cis*-dibenzoate (15·5 g.) was boiled under reflux for 4 hours in dry methanol (250 c.c.) containing sodium (0·2 g.). The solution was then steam-distilled, and the diol was isolated by continuous extraction of the residual aqueous solution with ether. Evaporation of the dried (Na_2SO_4) extract gave the *cis*-diol (6 g., 96%) as a non-crystallisable oil. Malachowski *et al.* (*loc. cit.*) reported m. p. 43°. The *trans*-dibenzoate (69 g.) in dry methanol (600 c.c.) containing sodium (0·2 g.) similarly gave the *trans*-diol (28 g., 99%), m. p. 62—64°, raised to 66° by crystallization from anhydrous ether. Malachowski *et al.* (*loc. cit.*) gave m. p. 67°.

(ii) Dimethyl *cis*-hexahydroterephthalate (4·1 g.) in dry ether (30 c.c.) was added slowly, with stirring, to a cooled solution of lithium aluminium hydride (1 g.) in dry ether (50 c.c.). After an hour, dilute sulphuric acid was added until, after shaking, no solid remained, and the ethereal layer was separated. The aqueous layer was continuously extracted with ether overnight, and the combined ethereal solutions were dried (K_2CO_3) and evaporated to give the *cis*-diol (2·7 g., 91%) as an oil; benzoylation of a portion gave the dibenzoate, m. p. and mixed m. p. 84°.

Derivatives of cis-**1 : 4-*Bishydroxymethyl*cyclo*hexane*.**—The *cis*-diol (0·5 g.), treated with toluene-*p*-sulphonyl chloride (1·45 g.) in pyridine (5 c.c.) for 20 hours at 0°, followed by precipitation with ice, gave the *ditoluene*-p-*sulphonate* (0·62 g., 40%), which crystallised from methanol in needles, m. p. 95° (Found: C, 58·3; H, 6·3; S, 13·9. $C_{22}H_{28}O_6S_2$ requires C, 58·4; H, 6·2; S, 14·2%). Similarly prepared, the *dimethanesulphonate* (74%) formed needles, m. p. 69°, from methanol (Found: C, 40·2; H, 6·75; S, 21·2. $C_{10}H_{20}O_6S_2$ requires C, 40·0; H, 6·7; S, 21·35%). The *cis*-diol (0·5 g.) and phenyl *iso*cyanate (1 g.), heated for 1 hour at 100°, gave the *bisphenylurethane* (0·95 g., 72%), which crystallised from benzene–light petroleum (b. p. 60—80°) in needles, m. p. 147—148° (Found: C, 69·2; H, 7·1; N, 7·3. $C_{22}H_{26}O_4N_2$ requires C, 69·1; H, 6·85; N, 7·3%).

Derivatives of trans-**1 : 4-*Bishydroxymethyl*cyclo*hexane*.**—Under conditions described for the *cis*-isomer, there were obtained the *ditoluene*-p-*sulphonate* (77%), needles, m. p. 162—163° (Found: C, 58·7; H; 6·4, S, 13·5%), the *dimethanesulphonate* (71%), needles, m. p. 158° (Found: C, 40·2; H, 6·9; S, 21·05%), and the *bisphenylurethane* (70%), plates, m. p. 197° (Found: C, 69·0; H, 6·5; N, 7·6%), all from acetone.

The *trans*-diol (pyridine–acetic anhydride) gave the *diacetate* (55%), needles, m. p. 70°, from aqueous methanol (Found: C, 63·2; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·2; H, 8·8%).

1 : 4-*Bisiodomethyl*cyclo*hexanes*.—(i) The *cis*-dimethanesulphonate (1 g.) was refluxed for 16 hours in acetone (25 c.c.), containing sodium iodide (2·5 g.). The precipitated sodium methanesulphonate (0·9 g.) was removed, and the filtrate evaporated. Water was added to the residue, and the iodide extracted into chloroform and dried (Na_2SO_4). Removal of solvent followed by distillation of the residual oil gave the cis-*di-iodide* (0·5 g., 41%) as a yellow liquid, b. p. 103—105°/10^{-4} mm., n_D^{29} 1·6082 (Found: C, 27·1; H, 4·1; I, 69·3. $C_8H_{14}I_2$ requires C, 26·4; H, 3·9; I, 69·7%).

(ii) The *trans*-dimethanesulphonate (0·35 g.) similarly gave the trans-*di-iodide* (0·4 g., 94%), which, however, solidified on the addition of water; it crystallised from methanol as fine needles, m. p. 77—78° (Found: C, 26·5; H, 4·0; I, 69·9%).

trans-**1 : 4-*Bisbromomethyl*cyclo*hexane*.**—The *trans*-ditoluene-*p*-sulphonate (0·25 g.) was refluxed for 16 hours in ethanol (10 c.c.) containing lithium bromide (0·2 g.). Ethanol was distilled off, and water added to precipitate a solid, which on crystallisation from aqueous methanol gave the *trans*-dibromide (0·1 g.), m. p. 55°. Malachowski *et al.* (*loc. cit.*) give m. p. 55°.

Hydrolysis of the trans-*Dimethanesulphonate*.—The dimethanesulphonate (11·5 g.) was boiled under reflux for 5 hours with 16% aqueous potassium hydroxide (50 c.c.), and the solution was then steam-distilled. The distillate was extracted with ether, dried (Na_2SO_4), and evaporated to give **4-*methylene*cyclo*hexylmethanol*** (0·4 g.), b. p. 128—130°/57 mm., n_D^{19} 1·4825 (Found: C, 76·3; H, 11·1%; ⌈0·95 by catalytic hydrogenation. $C_8H_{14}O$ requires C, 76·1; H, 11·2%; ⌈1·0). The **3 : 5-*dinitrobenzoate*** crystallised from methanol in needles, m. p. 97—98° (Found: C, 55·9; H, 5·0; N, 8·6. $C_{15}H_{16}O_6N_2$ requires C, 56·2; H, 5·0; N, 8·75%). The

residue from the steam-distillation was continuously extracted with ether to give the *trans*-diol (4 g., 73%), identified as ditoluene-*p*-sulphonate, m. p. and mixed m. p. 163°.

Hydrolysis of the cis-*Dimethanesulphonate*.—The dimethanesulphonate (1·1 g.), similarly hydrolysed, gave 4-methylene*cyclo*hexylmethanol (20 mg.) (3 : 5-dinitrobenzoate, m. p. and mixed m. p. 97—98°), and *cis*-diol (0·3 g.).

Ozonolysis of 4-*Methylene*cyclo*hexylmethanol*.—The alcohol (0·25 g.) in acetic acid (10 c.c.) was treated with ozonised oxygen for 15 minutes; absorption had then ceased. Zinc dust (2 g.) was added, and the mixture steam-distilled into aqueous 2 : 4-dinitrophenylhydrazine sulphate. The yellow precipitate was collected and chromatographed on alumina from benzene, to give impure formaldehyde 2 : 4-dinitrophenylhydrazone (70 mg.), m. p. 155°. The m. p. could not be raised by further treatment, but it was not depressed on admixture with an authentic sample, m. p. 165° (Found : C, 40·7; H, 3·2; N, 25·4. Calc. for $C_7H_6O_4N_4$: C, 40·0; H, 2·9; N, 26·7%). Light absorption : max. 3440 Å, ε 18,900 (in $CHCl_3$).

Monotoluene-p-*sulphonates of* 1 : 4-*Bishydroxymethyl*cyclo*hexane*.—(i) The *cis*-diol (3 g.), in chloroform–pyridine (1 : 1; 50 c.c.), was cooled to 0° and treated with toluene-*p*-sulphonyl chloride (4 g.) in the same solvent (50 c.c.), dropwise, with stirring, during 4 hours. Chloroform and pyridine were then removed under reduced pressure below 35° and the residue was dissolved in chloroform and washed with dilute sulphuric acid, aqueous hydrogen sodium carbonate, and water. After being dried (Na_2SO_4), the chloroform was removed, and the residue dissolved in a small volume of methanol and cooled to 0°. After filtration from a small quantity of ditoluene-*p*-sulphonate, removal of methanol gave the crude cis-*monotoluene*-p-*sulphonate* (3·1 g.) as a viscous yellow oil (Found : S, 9·05. $C_{15}H_{22}O_4S$ requires S, 10·7%). Reaction of a portion with *p*-nitrobenzoyl chloride in pyridine gave the cis-p-*nitrobenzoate–toluene*-p-*sulphonate*, needles (from methanol), m. p. 81° (Found : C, 59·6; H, 6·1; N, 3·2. $C_{22}H_{25}O_7NS$ requires C, 59·0; H, 5·6; N, 3·1%).

(ii) Interaction of the *trans*-diol (5 g.) with toluene-*p*-sulphonyl chloride (6·6 g.) under similar conditions gave the trans-*monotoluene*-p-*sulphonate* (2·9 g.) as a yellow oil (Found : S, 10·1%). Methanesulphonyl chloride in pyridine then gave the trans-*methanesulphonate–toluene*-p-*sulphonate*, needles (from methanol), m. p. 105° (Found : C, 51·1; H, 6·2; S, 17·0. $C_{16}H_{24}O_6S_2$ requires C, 51·0; H, 6·4; S, 17·0%).

Reaction of the cis-*Monotoluene*-p-*sulphonate with* 2 : 6-*Lutidine*.—The monotoluene-*p*-sulphonate (2·5 g.) and 2 : 6-lutidine (7 c.c.) were boiled under reflux for 2 hours, the initially homogeneous solution then having separated into two layers. Excess of concentrated hydrochloric acid was added, with cooling, and the solution extracted with ether. Evaporation of the dried (Na_2SO_4) extracts followed by distillation gave a strongly unsaturated product (0·3 g.), b. p. 120—130°/25 mm., n_D^{20} 1·4802, which was shown to be mainly 4-methylene*cyclo*hexylmethanol by preparation of the 3 : 5-dinitrobenzoate, m. p. and mixed m. p. 97—98°.

Hydrolysis of the trans-*Monotoluene*-p-*sulphonate*.—The monotoluene-*p*-sulphonate (2 g.) was boiled under reflux for 16 hours with 10% aqueous potassium hydroxide (10 c.c.); steam-distillation then removed unsaturated material but in quantity insufficient for identification. Continuous extraction of the alkaline solution with ether gave the *trans*-diol (0·7 g., 73%), identified as dimethanesulphonate, m. p. 158°.

trans-4-*Chloromethyl*cyclo*hexylmethanol*.—The *trans*-diol (10 g.) and fuming hydrochloric acid (13 c.c.; *d* 1·19) were heated at 100° for 20 hours (sealed tube). The product was extracted with chloroform, and the dried (Na_2SO_4) solution evaporated and distilled to give the trans-*monochloride* (7·2 g.), b. p. 75—90°/0·04 mm., n_D^{23} 1·4858—1·4908. A fraction, b. p. 78—82°/0·04 mm., n_D^{23} 1·4897, was analysed (Found : C, 59·2; H, 9·18; Cl, 21·4. $C_8H_{15}OCl$ requires C, 59·1; H, 9·30; Cl, 21·8%). It gave a p-*nitrobenzoate*, needles, m. p. 64—65°, from ethanol (Found : C, 58·2; H, 6·05; N, 4·4. $C_{15}H_{18}O_4NCl$ requires C, 57·8; H, 5·8; N, 4·5%).

Hydrolysis of trans-4-*Chloromethyl*cyclo*hexylmethanol*.—The monochloride (7·1 g.) was boiled under reflux for 30 hours with 10% aqueous potassium hydroxide (50 c.c.); the resulting suspension was steam-distilled and the distillate extracted with ether. Distillation of the dried (Na_2SO_4) extract gave a liquid (2·2 g.), b. p. 100—138°/20 mm., n_D^{18} 1·4801—1·4861, which was unsaturated and contained chlorine. Ozonolysis in acetic acid at room temperature, followed by steam-distillation with zinc, gave formaldehyde (dimedone derivative, m. p. and mixed m. p. 189—190°; 2 : 4-dinitrophenylhydrazone, m. p. 155°). The residual alkaline solution from the hydrolysis was continuously extracted with ether to give the *trans*-diol (2·7 g.), identified as the dimethanesulphonate, m. p. and mixed m. p. 158°.

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82. *Alicyclic Glycols. Part XI.* A Chemical Proof of the Configurations of the* 1 : 2-, 1 : 3-, *and* 1 : 4-*Dimethylcyclohexanes, and of the* 2-, 3-, *and* 4-*Methylcyclohexylmethanols.*

By G. A. Haggis and L. N. Owen.

From the dimethanesulphonates or ditoluene-*p*-sulphonates of the *cis*- and the *trans*-forms of the 1 : 2-, 1 : 3-, and 1 : 4-bishydroxymethyl*cyclo*hexanes, the corresponding isomers of the 1 : 2-, 1 : 3-, and 1 : 4-dimethyl*cyclo*hexanes have been synthesised, thus providing rigid chemical proof of the configurations of these hydrocarbons. Similarly, from the monohalides or monotoluene-*p*-sulphonates the corresponding isomers of the 2-, 3-, and 4-methyl*cyclo*hexylmethanols have been synthesised. The Auwers–Skita rules are confirmed for the 1 : 2- and 1 : 4-disubstituted *cyclo*hexanes, but must be reversed for the 1 : 3-compounds.

The assignment of configurations to disubstituted *cyclo*hexanes is best founded on methods such as the resolution of the *trans*-isomer (only applicable to symmetrically substituted 1 : 2- and 1 : 3-compounds), or the preferential formation of a bicyclic compound, such as an intramolecular dehydration product, from the *cis*-isomer (only applicable when there is no possibility of change of configuration during the reaction). When these or similar methods are not available, the Auwers–Skita rules have been widely used (Auwers, *Annalen*, 1920, **420**, 89; Auwers and Ottens, *Ber.*, 1924, **57**, 437; Skita, *Ber.*, 1920, **53**, 1792; 1922, **55**, 144). According to these, of a pair of *cis–trans*-isomers, the *cis*-compound has the higher boiling point, refractive index, and density; it is also usual that the *trans*-compound has a higher melting point and a lower solubility, and is the more stable of the two.

In cases where configurations have been independently established by rigorous methods, the few exceptions encountered with 1 : 2- and 1 : 4-compounds have usually been confined to occasional anomalies in the melting points of derivatives (see, *e.g.* Owen and Robins, *J.*, 1949, 320). With 1 : 3-compounds, however, the position is much less satisfactory (cf. Auwers and Ottens, *loc. cit.*). Thus the melting points of all the known derivatives of *cis*-1 : 3-bishydroxymethyl*cyclo*hexane are higher than those of the corresponding *trans*-isomers (Part IX, *J.*, 1953, **399**); many of the derivatives of *cyclo*hexane-1 : 3-diol show anomalous melting points (Clarke and Owen, *J.*, 1950, 2103); the resolvable *trans*-hexahydro*iso*phthalic acid has a lower melting point than the *cis*-form (Goodwin and Perkin, *J.*, 1905, **87**, 843); the resolvable *trans*-3 : 5-dimethyl*cyclo*hexanone has a higher refractive index than the *cis*-isomer (Braun and Haensel, *Ber.*, 1926, **59**, 1999; Braun and Anton, *Ber.*, 1927, **60**, 2438), and the same is true of the 3 : 5-dimethyl*cyclo*hexanols (Skita and Faust, *Ber.*, 1939, **72**, 1127). Another example of special interest is the preparation by Mousseron and Granger (*Bull. Soc. chim.*, 1938, **5**, 1618; 1946, 218) of an optically active 1 : 3-dimethyl*cyclo*hexane (which must therefore be *trans*) with a higher boiling point and refractive index than the inactive form, though the work can be criticised on the grounds that no yields or analytical data were recorded at any stage in their synthesis.

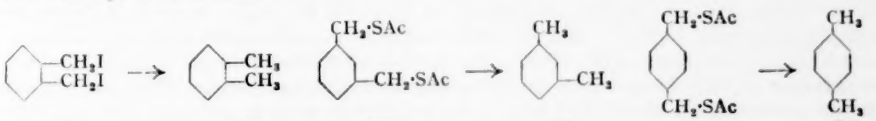
Hassel (for general references see Hassel and Ottar, *Acta Chem. Scand.*, 1947, **1**, 929; Hassel and Furberg, *ibid.*, 1950, **4**, 597; for diagrams see Birch, *Ann. Reports*, 1951, **48**, 192) has pointed out that in the more stable chair form of *cyclo*hexane the C–H bonds are of two types, and that a particular stereoisomer of a 1 : 3-disubstituted *cyclo*hexane is likely to correspond in spatial arrangement to that of the opposite stereoisomer of a 1 : 2- or a 1 : 4-compound. Beckett, Pitzer, and Spitzer (*J. Amer. Chem. Soc.*, 1947, **69**, 2488; Pitzer and Beckett, *ibid.*, p. 977; see also Prosen, Johnson, and Rossini, *J. Res. Nat. Bur. Stand.*, 1947, **39**, 173; Rossini and Spitzer, *Science*, 1947, **105**, 647), in emphasing these facts, have suggested that the Auwers–Skita rules, if applicable to 1 : 2- and 1 : 4-compounds, should be reversed for 1 : 3-disubstituted *cyclo*hexanes, and they have found thermodynamic evidence in favour of such a revision for the 1 : 3-dimethyl*cyclo*hexanes, thus supporting the observation of Mousseron and Granger (*loc. cit.*). In order to provide further chemical evidence, it was decided to study the synthesis of the stereoisomers of all

* Part X, preceding paper.

the dimethyl*cyclo*hexanes and methyl*cyclo*hexylmethanols by methods which would lead to a rigid proof of the configurations.

The dimethyl*cyclo*hexanes have usually been prepared by reduction of the corresponding xylenes under various conditions, but it is unlikely that any were obtained in a stereochemically pure form by the earlier workers. Miller and Piaux (*Bull. Soc. chim. Belg.*, 1932, **41**, 217; *Compt. rend.*, 1933, **197**, 412; 1935, **201**, 76), and also Forziati, Glasgow, Willingham, and Rossini (*J. Res. Nat. Bur. Stand.*, 1946, **36**, 129), carried out precision fractionations, and claimed to have obtained all six isomers in a pure state; their data for the 1 : 2- and the 1 : 3-compounds are in good agreement with those recorded by Bazhulin, Ukholin, Bulanova, Koperina, Plate, and Kazanskii (*Chem. Abs.*, 1950, **44**, 1332). The configurations were based only on the Auwers–Skita rules. The 2-, 3-, and 4-methyl*cyclo*hexylmethanols have been prepared by reduction of the 2-, 3-, and 4-methyl*cyclo*hexanecarboxylic esters with sodium and alcohol (Perkin and Pope, *J.*, 1908, **93**, 1078; Skita, *Annalen*, 1923, **431**, 1; Mousseron, Granger, Bourrel, and Cellier, *Bull. Soc. chim.*, 1946, 640), but owing to the occurrence of epimerisation under such conditions it is unlikely that stereochemically pure products were obtained even when stereochemically pure esters were used. When the reduction is effected by hydrogenation over a chromite catalyst, however, little or no epimerisation occurs, and by purification through crystalline derivatives both stereoisomers of the 2-methyl (Macbeth, Mills, and Simmonds, *J.*, 1949, 1011), both of the 4-methyl (Cooke and Macbeth, *J.*, 1939, 1245), and one of the 3-methyl (Darling, Macbeth, and Mills, personal communication) alcohols have been obtained, but again the accepted configurations are founded only on physical properties.

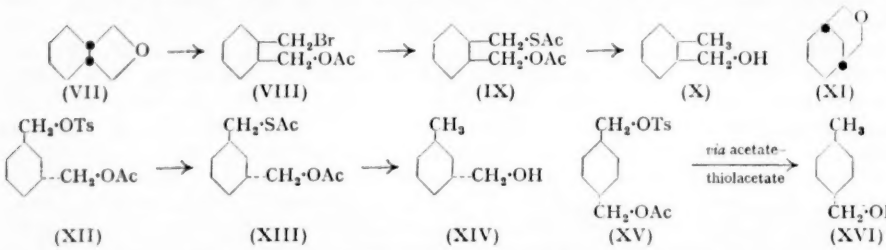
The syntheses now to be described are all based on derivatives of the various bishydroxymethyl*cyclo*hexanes, the configurations of which have been rigidly established (Parts VIII, IX, and X, preceding papers); the reactions involved are such that no change of configuration can occur, and that of the final hydrocarbon or alcohol is therefore known with certainty in each case.



(I) (II) (III) (IV) (V) (VI)

Hydrogenation of *cis*-1 : 2-bisiodomethyl*cyclo*hexane (I), the configuration of which is known from its preparation from the *cis*-1 : 2-dimethanesulphonate (Part VIII, *loc. cit.*), gave *cis*-1 : 2-dimethyl*cyclo*hexane (II); the *trans*-isomer of (I) similarly gave the *trans*-hydrocarbon. The physical properties of the products were in good agreement with those recorded by Forziati *et al.* (*loc. cit.*), and the earlier configurations are therefore confirmed. The method, however, suffered from the practical disadvantage that the large amount of methanol required as solvent in the hydrogenation caused difficulty in the isolation of the rather volatile hydrocarbon, and a different route was adopted for the 1 : 3- and 1 : 4-compounds. This was based on the conversion of a primary toluene-*p*-sulphonate into a thiolacetate (method of Chapman and Owen, *J.*, 1950, 579), followed by desulphurisation with Raney nickel, but although a smaller amount of solvent could then be used in the final stage, the separation of the pure hydrocarbon was still attended by considerable loss of material. Sufficient was obtained, however, from each experiment to render identification quite certain. The ditoluene-*p*-sulphonate of *cis*-1 : 3-bishydroxymethyl*cyclo*hexane gave the *cis*-bisthiolacetate (III) and thence *cis*-1 : 3-dimethyl*cyclo*hexane (IV); similarly, *cis*-1 : 4-dimethyl*cyclo*hexane (VI) was prepared from the *cis*-1 : 4-ditoluene-*p*-sulphonate, *via* the bisthiolacetate (V), and the two *trans*-hydrocarbons through the corresponding *trans*-intermediates. The properties of the 1 : 4-hydrocarbons agreed with those recorded by Forziati *et al.* (*loc. cit.*), but with the 1 : 3-dimethyl*cyclo*hexanes the properties of our *cis*-hydrocarbon agreed with those of their so-called *trans*-isomer and *vice versa*. It is therefore certain that the original assignments of configuration are correct for the 1 : 2- and 1 : 4-hydrocarbons, but that, in agreement with Mousseron and Granger (*loc. cit.*) and Pitzer *et al.* (*loc. cit.*), they must be reversed for the 1 : 3-isomers.

In order to apply the thiolacetate method to the unambiguous synthesis of the various methyl*cyclo*hexylmethanols a monohalide or monotoluene-*p*-sulphonate of the appropriate bishydroxymethyl*cyclo*hexane was required. In the 1 : 2-series (Part VIII, *loc. cit.*) it has been shown that fission of *cis*-octahydro*iso*benzofuran (VII) with acetyl bromide gives *cis*-2-bromomethyl*cyclo*hexylmethyl acetate (VIII). When the latter was treated with potassium thiolacetate it gave *cis*-2-(acetylthiomethyl)*cyclo*hexylmethyl acetate (IX), which on desulphurisation with Raney nickel, followed by deacetylation, then gave *cis*-2-methyl*cyclo*hexylmethanol (X). A similar series of reactions was used to synthesise the *trans*-alcohol from *trans*-octahydro*iso*benzofuran. The properties of the products, and of



their derivatives, agreed with those of the same configuration described by the earlier workers, and the validity of the Auwers–Skita rules in this instance is thereby proved.

In the 1 : 3-series, fission of 3-oxa*bicyclo*[3 : 3 : 1]nonane (XI) with acetyl bromide has been shown (Part IX, *loc. cit.*) to give *cis*-3-bromomethyl*cyclo*hexylmethyl acetate, the analogue of (VIII). This was converted through the corresponding intermediates into *cis*-3-methyl*cyclo*hexylmethanol. Unlike the position in the 1 : 2-series, a similar synthesis of the *trans*-3-methyl alcohol was not possible because a *trans*-fused tetrahydropyran system stereoisomeric with (XI) cannot be formed (cf. Part IX, *loc. cit.*). *trans*-1 : 3-Bishydroxymethyl*cyclo*hexane, however, can be converted into a crude monotoluene-*p*-sulphonate; acetylation of this gave (XII), which with potassium thiolacetate gave the *trans*-acetate–thiolacetate (XIII), from which *trans*-3-methyl*cyclo*hexylmethanol (XIV) was obtained. The properties of the *cis*-alcohol and of its derivatives were in excellent agreement with those found by Darling, Macbeth, and Mills for their alcohol of undetermined configuration (we are grateful to Professor Macbeth and Dr. Mills for informing us of their experiments, and for providing specimens of their derivatives), but it had a lower refractive index than the *trans*-alcohol and thus provides a further example of the breakdown of the Auwers–Skita rules when applied to 1 : 3-compounds.

In the 1 : 4-series, no cyclic oxide had been obtained, and the route through the monotoluene-*p*-sulphonate of the diol was therefore followed. Acetylation of the *trans*-monoester gave the *trans*-acetate–toluene-*p*-sulphonate (XV), from which *trans*-4-methyl*cyclo*hexylmethanol (XVI) was prepared *via* the *trans*-acetate–thiolacetate. The properties of this alcohol and of its derivatives corresponded to those of the isomer previously designated *trans* on the basis of the Auwers–Skita rules.

As a result of these observations it is clear that the rules can be confidently applied to 1 : 2- and 1 : 4-disubstituted *cyclo*hexanes. Although the available evidence strongly suggests that they can be applied in the reverse sense to 1 : 3-compounds, the provision of further well-authenticated examples is desirable before the generality of such a procedure can be recognised.

Experimental

(Starting materials were prepared by the methods described in Parts VIII—X, *locc. cit.*)

1 : 3-*Di*(*acetylthiomethyl*)cyclo*hexane*.—(i) A solution of the ditoluene-*p*-sulphonate of *cis*-1 : 3-bishydroxymethyl*cyclo*hexane (5 g.) and potassium thiolacetate (4 g.) in ethanol (50 c.c.) was made slightly acid with thiolacetic acid (0·1 c.c.), and boiled under reflux for 2 hours. Most of the ethanol was then distilled off, and the residue diluted with water and extracted with chloroform. The extracts were washed with water, dried (Na_2SO_4), and distilled to give *cis*-1 : 3-*di*(*acetylthiomethyl*)cyclo*hexane* (2·05 g.), b. p. 120—124°/0·01 mm., n_D^{19} 1·5355 (Found :

C, 55·1; H, 7·75; S, 24·85. $C_{12}H_{20}O_2S_2$ requires C, 55·35; H, 7·7; S, 24·6%). (ii) The *trans*-1 : 3-ditoluene-*p*-sulphonate (2·8 g.) with potassium thiolacetate (2·5 g.) similarly gave trans-1 : 3-*di*(*acetylthiomethyl*)cyclo*hexane* (1·05 g.), b. p. 130—135°/0·03 mm., n_D^{23} 1·5285 (Found : C, 55·05; H, 7·7; S, 23·7%).

1 : 4-*Di*(*acetylthiomethyl*)cyclo*hexane*.—(i) Reaction of the ditoluene-*p*-sulphonate of *cis*-1 : 4-bishydroxymethyl*cyclo*hexane (4 g.) with potassium thiolacetate (3 g.) in a similar way gave the cis-1 : 4-*bisthiolacetate* (1·7 g.), b. p. 123—125°/0·01 mm., n_D^{19} 1·5348 (Found : C, 54·3; H, 7·9; S, 23·4%). (ii) The *trans*-1 : 4-ditoluene-*p*-sulphonate (9·9 g.) with potassium thiolacetate (7·5 g.) under the same conditions gave the trans-1 : 4-*bisthiolacetate* (4 g.), needles, m. p. 51—52° (Found : C, 55·2; H, 7·8; S, 24·9%), from light petroleum (b. p. 40—60°).

1 : 2-*Dimethyl*cyclo*hexane*.—(i) A solution of *cis*-1 : 2-bisiodomethyl*cyclo*hexane (10·5 g.) and potassium acetate (5·8 g.) in methanol (200 c.c.) was hydrogenated at 1 atm. over a platinic oxide catalyst (0·3 g.). When no more gas was absorbed (10 hours) the solution was filtered and diluted with much water. The upper layer was collected, washed thoroughly with water to remove methanol (considerable losses occurred), and dried (K_2CO_3). Distillation then gave *cis*-1 : 2-dimethyl*cyclo*hexane (0·5 g.), b. p. 129—130°, n_D^{19} 1·4360. Forziati *et al.* (*loc. cit.*) gave b. p. 129·7°, n_D^{20} 1·4360. (ii) Similar hydrogenation of the *trans*-di-iodide (17 g.) in methanol (500 c.c.) containing potassium acetate (12 g.) gave the *trans*-hydrocarbon (2·1 g.), b. p. 123°, n_D^{18} 1·4280. Forziati *et al.* recorded b. p. 123·4°, n_D^{20} 1·4270.

1 : 3-*Dimethyl*cyclo*hexane*.—(i) A solution of *cis*-1 : 3-di(acetylthiomethyl)*cyclo*hexane (3 g.) in methanol (50 c.c.) was boiled under reflux for 2 hours with freshly prepared Raney nickel (*ca.* 20 g.). The filtered solution was then diluted with water, and the hydrocarbon washed and dried as described above. Distillation gave *cis*-1 : 3-dimethyl*cyclo*hexane (0·3 g.), b. p. 120—121°, n_D^{20} 1·4235. Forziati *et al.* gave b. p. 120·1°, n_D^{20} 1·4229, for their "*trans*"-compound. (ii) The *trans*-1 : 3-bisthiolacetate (1·05 g.) similarly gave the *trans*-hydrocarbon (0·05 g.), b. p. 124°, n_D^{24} 1·4287. Forziati *et al.* gave b. p. 124·4°, n_D^{25} 1·4284, for their "*cis*"-compound.

1 : 4-*Dimethyl*cyclo*hexane*.—(i) Under similar conditions the *cis*-1 : 4-bisthiolacetate (1·4 g.) gave *cis*-1 : 4-dimethyl*cyclo*hexane (0·1 g.), b. p. 123—124°, n_D^{18} 1·4291. Forziati *et al.* gave b. p. 124·3°, n_D^{20} 1·4297. (ii) The *trans*-1 : 4-bisthiolacetate (4 g.) gave the *trans*-hydrocarbon (0·35 g.), b. p. 119—119·5°, n_D^{22} 1·4210. Forziati *et al.* recorded b. p. 119·3°, n_D^{20} 1·4209.

2-(*Acetylthiomethyl*)cyclo*hexylmethyl Acetate*.—(i) A solution of *cis*-2-bromomethyl*cyclo*hexylmethyl acetate (1·5 g.), potassium thiolacetate (1·3 g.), and thiolacetic acid (0·1 g.) in ethanol (50 c.c.) was boiled under reflux for 3 hours. The product was isolated as described for the bisthiolacetates above, and on distillation gave the cis-*acetate–thiolacetate* (0·8 g.), b. p. 105—110°/0·1 mm., n_D^{20} 1·5016 (Found : C, 58·45; H, 8·2; S, 13·0. $C_{12}H_{20}O_3S$ requires C, 59·0; H, 8·25; S, 13·1%). (ii) Similar treatment of *trans*-2-bromomethyl*cyclo*hexylmethyl acetate (2·8 g.) with potassium thiolacetate (1·8 g.) gave the trans-*acetate–thiolacetate* (2·35 g.), b. p. 105—108°/0·1 mm., n_D^{20} 1·4992 (Found : C, 57·9; H, 8·2; S, 12·9%).

3-(*Acetylthiomethyl*)cyclo*hexylmethyl Acetate*.—(i) Reaction of *cis*-3-bromomethyl*cyclo*hexylmethyl acetate (3·1 g.) with potassium thiolacetate (1·8 g.) similarly gave the cis-*acetate–thiolacetate* (1·8 g.), b. p. 115—117°/0·3 mm., n_D^{22} 1·4978 (Found : C, 58·45; H, 8·2; S, 13·5%). (ii) Monotoluene-*p*-sulphonation of *trans*-1 : 3-bishydroxymethyl*cyclo*hexane (3 g.) under the conditions described for the *cis*-isomer (Part IX, *loc. cit.*) gave a crude monotoluene-*p*-sulphonate (2 g.), which was characterised as the p-*nitrobenzoate–toluene*-p-*sulphonate* of the diol; this formed a microcrystalline powder, m. p. 97—98°, from light petroleum (b. p. 60—80°) (Found : C, 58·7; H, 5·8. $C_{22}H_{25}O_7NS$ requires C, 59·0; H, 5·6%). The monotoluene-*p*-sulphonate (1·9 g.) was acetylated with acetic anhydride (0·8 g.) in pyridine (10 c.c.), and the resulting product (2·2 g.) was boiled under reflux with potassium thiolacetate (0·8 g.) in ethanol (10 c.c.) for 2 hours to give the crude *trans*-acetate–thiolacetate (0·92 g.), b. p. 110—130°/0·1 mm., n_D^{22} 1·4951 (Found : S, 10·9%).

4-(*Acetylthiomethyl*)cyclo*hexylmethyl Acetate*.—The monotoluene-*p*-sulphonate of *trans*-1 : 4-bishydroxymethyl*cyclo*hexane (1·7 g.) was acetylated with acetic anhydride (0·7 g.) in pyridine (10 c.c.) to give the trans-*acetate–toluene*-p-*sulphonate* as a yellow oil (Found : S, 9·9. $C_{17}H_{24}O_5S$ requires S, 9·4%). This (1·6 g.) was boiled under reflux with potassium thiolacetate (0·7 g.) in methanol (10 c.c.) for 2 hours, and gave the crude *trans*-acetate–thiolacetate (0·8 g.), b. p. 130—150°/0·5 mm., n_D^{22} 1·4921 (Found : S, 11·3%).

2-*Methyl*cyclo*hexylmethanol*.—(i) A solution of *cis*-2-(acetylthiomethyl)*cyclo*hexylmethyl acetate (0·75 g.) in ethanol (50 c.c.) was boiled under reflux for 2 hours with Raney nickel (*ca.* 5 g.) and then filtered. Sodium hydroxide (2 g.) was then added, and after being boiled under reflux for a further 2 hours the solution was evaporated to small bulk under reduced pressure.

The residue was extracted with ether, and furnished *cis*-2-methyl*cyclo*hexylmethanol (0·2 g.), b. p. 110—115°/30 mm., n_D^{20} 1·4689, characterised as the 3 : 5-dinitrobenzoate, m. p. 91·5—92·5°. Macbeth, Mills, and Simmonds (*loc. cit.*) give b. p. 83°/10 mm., n_D^{20} 1·4690, and m. p. 92—93°, respectively.

(ii) Similar treatment of the *trans*-acetate–thiolacetate (2·2 g.) gave *trans*-2-methyl*cyclo*hexylmethanol (0·5 g.), b. p. 95—98°/14 mm., n_D^{16} 1·4652, characterised as the *p*-nitrobenzoate, m. p. 58—59°, and the 3 : 5-dinitrobenzoate, m. p. 68—69°. Macbeth, Mills, and Simmonds (*loc. cit.*) give b. p. 80°/10 mm., n_D^{20} 1·4633, and m. p.s 59—60° and 68·5—69·5° respectively.

3-*Methyl*cyclo*hexylmethanol*.—(i) A solution of *cis*-3-(acetylthiomethyl)*cyclo*hexylmethyl acetate (1·6 g.) in methanol (25 c.c.) was boiled with Raney nickel (*ca.* 15 g.) for 2 hours under reflux. The solution was filtered, sodium hydroxide (1 g.) was added, and after a further 2 hours' boiling the bulk of the methanol was distilled off, and the residue was diluted with water. Extraction with light petroleum (b. p. 40—60°) gave cis-3-*methyl*cyclo*hexylmethanol* (0·63 g.), b. p. 92—94°/16 mm., n_D^{18} 1·4598 (Found: C, 74·45; H, 12·55. $C_8H_{16}O$ requires C, 74·95; H, 12·5%). The 3 : 5-*dinitrobenzoate* formed plates, m. p. 81—82°, from methanol (Found: C, 55·9; H, 5·6; N, 9·1. $C_{15}H_{18}O_6N_2$ requires C, 55·9; H, 5·6; N, 8·7%), and the *phenylurethane*, needles, m. p. 71—72°, from light petroleum (b. p. 60—80°) (Found: C, 72·9; H, 8·6; N, 5·6. $C_{15}H_{21}O_2N$ requires C, 72·8; H, 8·6; N, 5·7%). The m. p.s of these derivatives were not depressed on admixture with those of the m. p.s 81·5—82° and 73·5—74·5°, respectively, kindly provided by Professor Macbeth.

(ii) From the crude *trans*-acetate–thiolacetate (0·85 g.) there was similarly obtained trans-3-*methyl*cyclo*hexylmethanol* (0·21 g.), b. p. 112—114°/35 mm., n_D^{22} 1·4628 (Found: C, 74·6; H, 12·7%). The 3 : 5-*dinitrobenzoate* formed needles, m. p. 77—78°, from methanol (Found: C, 55·8; H, 5·7; N, 9·0%), and the α-*naphthylurethane*, nodules, m. p. 84—85°, from light petroleum (b. p. 60—80°) (Found: C, 76·4; H, 7·9; N, 4·8. $C_{19}H_{23}O_2N$ requires C, 76·7; H, 7·8; N, 4·7%). The m. p. of the 3 : 5-dinitrobenzoate was depressed to 60—63° on admixture with the *cis*-isomer.

4-*Methyl*cyclo*hexylmethanol*.—Crude *trans*-4-(acetylthiomethyl)*cyclo*hexylmethyl acetate (0·7 g.) on similar treatment gave *trans*-4-methyl*cyclo*hexylmethanol (0·2 g.), b. p. 99—101°/23 mm., n_D^{22} 1·4538, characterised as the 3 : 5-dinitrobenzoate, m. p. 111°, and the α-naphthylurethane, m. p. 110°. Cooke and Macbeth (*loc. cit.*) give b. p. 74°/3 mm., n_D^{20} 1·4578, and m. p.s 112° and 110·5°, respectively.

We thank Professor R. P. Linstead, C.B.E., F.R.S., for his interest in this and the preceding three papers, and the Department of Scientific and Industrial Research for a maintenance grant (to G. A. H.). All the microanalyses were carried out in the Micro-analytical Laboratory of this Department (Mr. F. H. Oliver).

Organic Chemistry Department, Imperial College of Science and Technology, South Kensington, London, S.W.7. [*Received, September 15th*, 1952.]

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83. *Experiments on the Preparation of Indolocarbazoles. Part VI.* Compounds from Two of the Amino-1-phenylbenzotriazoles.*

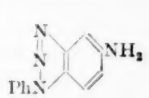
By A. R. Katritzky and S. G. P. Plant.

5-Amino-1-phenyl- and 1-*p*-aminophenyl-benzotriazole have been converted into a number of substances from which indolocarbazoles could theoretically be formed by a combination of a known carbazole synthesis with the Graebe–Ullmann reaction. Although some of these gave triazolo(5′ : 4′-3 : 4)carbazoles, the complete synthesis of an indolocarbazole along these lines has not been effected.

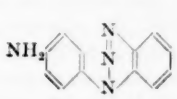
Many carbazole derivatives have been obtained by the Graebe–Ullmann reaction (*Annalen*, **1896**, **291**, 16), involving the elimination of nitrogen from the appropriate 1-phenylbenzotriazole. There are other well-known carbazole syntheses which also require an aromatic primary amine as starting material. It seemed possible, therefore, that indolocarbazoles would result from amino-1-phenylbenzotriazoles by suitable combinations of these syn-

* Part V, *J.*, 1953, 116.

thetical processes. With this end in view a study has been made of several derivatives of the comparatively readily accessible 5-amino-1-phenylbenzotriazole (I) and 1-*p*-aminophenylbenzotriazole (II).



(I)



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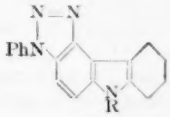

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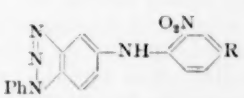
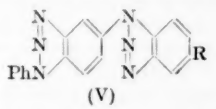


(IV)

Tetrahydrocarbazoles have been prepared by applying the Fischer indole synthesis to phenylhydrazines and *cyclo*hexanone, and it was hoped to extend this method, but the requisite hydrazine could not be obtained from either of the bases (I and II) by the usual processes.

From the base (I) the substituted 5-anilino-1-phenylbenzotriazoles (IV; R = NO_2, CN, Ac, and Cl) were prepared, although the yield of one of them (IV; R = Cl) was very small, and the first three were converted into the bistriazoles (V; R = NO_2, CN, and Ac). The compound (V; R = CN) has already been prepared by an alternative route by Coker, Plant, and Turner (*J.*, 1951, 110) who were unable to effect transformation into a cyano-



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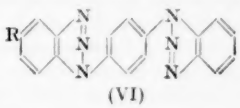

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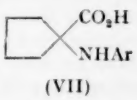
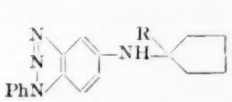


(VII)

indolocarbazole by a double Graebe–Ullmann reaction. The larger quantity of the substance now available has made it possible to study this process in more detail, as well as with the compound (V; R = Ac), albeit unsuccessfully. The compound (V; R = NO_2), obtained in less satisfactory yields, was, in consequence, not further examined because the presence of a nitro-group is known to affect the Graebe–Ullmann reaction adversely (Preston, Tucker, and Cameron, *J.*, 1942, 500). The isomeric bistriazoles (VI; R = CN and Ac) were prepared similarly from the base (II), but, since the overall yields were small and this type of bistriazole has already been examined by Clifton and Plant (*J.*, 1951, 461), they were not further studied.

In contrast to the synthesis of carbazoles from (VII) (Plant and Facer, *J.*, 1925, **127**, 2037; Oakeshott and Plant, *J.*, 1926, 1210; 1927, 484), alkali fusion of the acids (VIII; R = CO_2H) and (IX) and the amide (VIII; R = $CO{\cdot}NH_2$) failed to give the expected carbazoles or indolocarbazoles.



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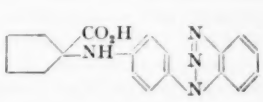
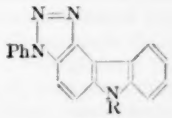


(IX)



(X)

In an extension of a known method for the preparation of tetrahydrocarbazoles (D.R.-P. 374,098; *Chem. Zentr.*, 1923, IV, 724; Campbell and McCall, *J.*, 1950, 2870), the base (I) reacted with 2-chloro*cyclo*hexanone to give a product for which there are two possible structures, but on theoretical grounds and from analogy with related reactions (see, *e.g.*, Tomlinson, *J.*, 1951, 809; Hall and Plant, Part V) it must be regarded as 5 : 6 : 7 : 8-tetrahydro-1′-phenyltriazolo(5′ : 4′-3 : 4)carbazole (III; R = H). It was hoped that a Graebe–Ullmann reaction would occur during the dehydrogenation of this substance with palladium–charcoal above 300°, but the products were unsatisfactory. Under some conditions carbazole appeared to be formed, and it is significant that Tomlinson (*loc. cit.*) observed that carbazole resulted from the dehydrogenation of products obtained by applying a double Fischer indole synthesis to bis*cyclo*hexanone *p*-phenylenedihydrazone. Conversion into 1′-phenyltriazolo(5′ : 4′-3 : 4)carbazole (X; R = H) was effected with chloranil in boiling xylene (cf. Barclay and Campbell, *J.*, 1945, 530), but all attempts to convert this

into indolo(2′ : 3′-3 : 4)carbazole have failed. Nothing pure could be isolated in attempts to condense the base (II) with 2-chloro*cyclo*hexanone.

The degree of success which attends Graebe–Ullmann reactions varies widely among closely related substances. With this in mind the benzylidene derivative of the base (I) was reduced to 5-benzylamino-1-phenylbenzotriazole, the nitrosamine from which was converted directly into 9-benzyl-5 : 6 : 7 : 8-tetrahydro-1′-phenyltriazolo(5′ : 4′-3 : 4)carbazole (III; R = Ph·CH_2) by reduction with zinc in warm acetic acid in the presence of *cyclo*hexanone, but attempts to effect dehydrogenation to the compound (X; R = Ph·CH_2) and a Graebe–Ullmann change have not succeeded. The nitrosamine from 1-*p*-benzylaminophenylbenzotriazole, from the base (II), did not give a tetrahydrocarbazole derivative under similar conditions, no doubt because even at 15—20° zinc and acetic acid reduced it to the original benzylamino-compound in good yield.

Experimental

2 : 4′-*Dinitrodiphenylamine*.—The following method was found to be more convenient than any in the literature for the preparation of this compound in substantial amounts. A mixture of *p*-nitroaniline (90 g.), *o*-chloronitrobenzene (75 g.), potassium carbonate (75 g.), copper powder (3 g.), and potassium iodide (3 g.) was rapidly heated to 200°. After the vigorous reaction had subsided, the temperature was raised to 215° for 3 minutes, and the whole poured into a large enamelled dish and broken up while still warm. The solid was agitated with a hot mixture of dilute hydrochloric acid and ethanol, and the dried residue extracted with boiling toluene (5 l.), from which 2 : 4′-dinitrodiphenylamine (92 g.) separated on cooling; recrystallisation from glacial acetic acid gave brick red needles, m. p. 219—220°.

Substituted 5-Anilino-1-phenylbenzotriazoles (IV).—After a mixture of 5-amino-1-phenylbenzotriazole, m. p. 158° (5 g., prepared by a method essentially the same as that of Beretta, *Gazzetta*, 1925, **55**, 788), 1-chloro-2 : 4-dinitrobenzene (5·5 g.), and anhydrous sodium acetate (5 g.) had been heated on a steam-bath for 2 hours, the whole extracted with dilute hydrochloric acid, and the dried residue crystallised from acetic acid, 5-(2 : 4-dinitroanilino)-1-phenylbenzotriazole (6·2 g.) was obtained in orange needles, m. p. 229—230° (Found: C, 57·0; H, 3·6. Calc. for $C_{18}H_{12}O_4N_6$: C, 57·4; H, 3·2%). The substance is evidently the same as that (m. p. 228°) prepared by Manjunath (*J. Indian Chem. Soc.*, 1927, **4**, 271) and called "1-*p*-2′ : 4′-dinitroanilinophenylbenzotriazole." In early preparations 5-amino-1-phenylbenzotriazole was obtained in an unstable polymorphic form, m. p. 128°.

The following were similarly prepared: 5-(4-*cyano*-2-*nitroanilino*)-1-*phenylbenzotriazole* (from 4-chloro-3-nitrobenzonitrile; reaction time, 4½ hours), orange-red needles (yield, 58%), m. p. 200° (rapid heating; on slow heating it changed to a yellow form, m. p. 209°) (from acetic acid, after purification by adsorption from benzene on alumina) (Found: C, 63·6; H, 3·4. $C_{19}H_{12}O_2N_6$ requires C, 64·0; H, 3·4%); and 5-(4-*acetyl*-2-*nitroanilino*)-1-*phenylbenzotriazole* (from 4-bromo-3-nitroacetophenone with the addition of copper powder; reaction temperature, 170° for 1 hour), orange crystals (yield, 30%), m. p. 205° (from toluene, after adsorption from benzene on alumina) (Found: C, 64·0; H, 4·0. $C_{20}H_{15}O_3N_5$ requires C, 64·3; H, 4·0%).

After a mixture of 5-amino-1-phenylbenzotriazole (6 g.), 2 : 5-dichloronitrobenzene (5·1 g.), potassium carbonate (3 g.), and amyl alcohol (30 c.c.) with small amounts of potassium iodide and copper powder had been refluxed for 5 hours and the solvent removed in steam, 5-(4-*chloro*-2-*nitroanilino*)-1-*phenylbenzotriazole* (0·08 g.) was isolated from the residue by adsorption from benzene on alumina, and obtained from toluene in scarlet needles, m. p. 201—202° (Found: C, 59·4; H, 3·5. $C_{18}H_{12}O_2N_5Cl$ requires C, 59·1; H, 3·3%).

Substituted 5-(Benzotriazol-1-yl)-1-phenylbenzotriazoles (V).—After crystalline sodium sulphide (1 g.) in water (1 c.c.) had been added to 5-(2 : 4-dinitroanilino)-1-phenylbenzotriazole (1 g.) in boiling ethanol (30 c.c.), the whole was boiled for 5 minutes and filtered. The solid which separated from the filtrate on cooling was immediately treated in boiling ethanol first with aqueous sodium nitrite (0·5 c.c. of 50%) and then with concentrated hydrochloric acid (1 c.c.). When the precipitate was crystallised from acetic acid, 5-(5-*nitrobenzotriazol*-1-*yl*)-1-*phenylbenzotriazole* (0·05 g.) separated in colourless prisms, m. p. 314° (Found: C, 59·9; H, 3·2. $C_{18}H_{11}O_2N_7$ requires C, 60·5; H, 3·1%).

Sodium hydrosulphite (dithionite) (12 g.) was gradually added to a boiling solution of 5-(4-cyano-2-nitroanilino)-1-phenylbenzotriazole (4 g.) in acetic acid (100 c.c.), and the whole boiled for 5 minutes. The hot mixture was filtered under suction, and sodium nitrite (1·2 g.) in water (2·5 c.c.) added dropwise to the boiling filtrate. The 5-(5-cyanobenzotriazol-1-yl)-1-

phenylbenzotriazole (3·5 g.) which separated on cooling was obtained from acetic acid in colourless prisms, m. p. 311°, identical (mixed m. p.) with the substance prepared by Coker, Plant, and Turner (*loc. cit.*) by another route. Prepared like the cyano-compound, 5-(5-*acetylbenzotriazol*-1-*yl*)-1-*phenylbenzotriazole* (yield, 60%) crystallised from acetic acid in pale yellow prisms, m. p. 295° (Found: N, 23·6. $C_{20}H_{14}ON_6$ requires N, 23·7%).

Substituted 1-p-*Anilinophenylbenzotriazoles*.—A mixture of 1-*p*-aminophenylbenzotriazole (1 g.; prepared from 2 : 4′-dinitrodiphenylamine; cf. Nietzki and Baur, *Ber.*, 1895, **28**, 2977), 1-chloro-2 : 4-dinitrobenzene (1·1 g.), and anhydrous sodium acetate (1 g.) was heated for an hour on the steam-bath. After the whole had been ground with ethanol–dilute hydrochloric acid, the residue was twice recrystallised from acetic acid, and 1-p-(2 : 4-*dinitroanilino*)*phenylbenzotriazole* (0·9 g.) obtained in orange needles, m. p. 248° (Found: C, 58·1; H, 3·3%).

The following were similarly prepared: 1-p-(4-*cyano*-2-*nitroanilino*)*phenylbenzotriazole* (from 4-chloro-3-nitrobenzonitrile, with potassium carbonate and a little copper powder instead of sodium acetate; reaction time, 3½ hours), orange prisms (yield, 23%), m. p. 246° (from acetic acid) (Found: C, 63·9; H, 3·5%), and 1-p-(4-*acetyl*-2-*nitroanilino*)*phenylbenzotriazole* (from 4-bromo-3-nitroacetophenone with copper powder; reaction temperature, 180° for 1 hour), yellow prisms (yield, 22%), m. p. 225—227° (from ethanol, after adsorption from benzene on alumina) (Found: C, 64·2; H, 3·8%).

Substituted 1-p-(*Benzotriazol*-1-*yl*)*phenylbenzotriazoles* (VI).—Prepared as described above for the isomeric compounds 1-p-(5-*cyanobenzotriazol*-1-*yl*)*phenylbenzotriazole* (yield, 38%) separated from nitrobenzene in colourless prisms, m. p. above 360°, containing solvent of crystallisation (Found: C, 64·8; H, 3·3. $C_{19}H_{11}N_7,C_6H_5O_2N$ requires C, 65·2; H, 3·5%), and 1-p-(5-*acetylbenzotriazol*-1-*yl*)*phenylbenzotriazole* (yield, 70%) from acetic acid in orange prisms, m. p. 269—271° (Found: N, 23·9%).

5-(1-*Carboxy*cyclo*pentylamino*)-1-*phenylbenzotriazole* (VIII; R = CO_2H) *and* 1-p-(1-*Carboxy*-cyclo*pentylamino*)*phenylbenzotriazole* (IX).—When *cyclo*pentanone (2·25 g.) was gradually added to a solution of 5-amino-1-phenylbenzotriazole (5 g.) in acetic acid (25 c.c.) which had been treated with potassium cyanide (2 g.) in water (5 c.c.), and the whole then kept at 40—45° for 6 hours, 5-(1-*cyano*cyclo*pentylamino*)-1-*phenylbenzotriazole* (6·5 g.), colourless plates, m. p. 139° (from ethanol), separated (Found: C, 71·0; H, 5·8. $C_{18}H_{17}N_5$ requires C, 71·3; H, 5·6%). On being refluxed with concentrated hydrochloric acid for 5 hours it was converted back to 5-amino-1-phenylbenzotriazole. After a solution of the cyano-compound (6·5 g.) in concentrated sulphuric acid (65 c.c.) had been left at room temperature for 2 days and then poured on ice, the addition of ammonia in the cold precipitated 5-(1-*carbamyl*cyclo*pentylamino*)-1-*phenylbenzotriazole* (6 g.), colourless prisms, m. p. 228° (from amyl alcohol) (Found: C, 66·9; H, 6·0; N, 22·2. $C_{18}H_{19}ON_5$ requires C, 67·3; H, 5·9; N, 21·8%). In early experiments a more soluble, unstable polymorphic form of the amide was obtained from aqueous ethanol in colourless prisms, m. p. 210°. The amide (5·3 g.) was refluxed for 6 hours with concentrated hydrochloric acid (53 c.c.), the whole evaporated to dryness, the residue dissolved in aqueous sodium hydroxide, and the filtered solution acidified with acetic acid. The precipitated 5-(1-*carboxy*-cyclo*pentylamino*)-1-*phenylbenzotriazole* (1·9 g.) separated from aqueous ethanol in colourless needles, m. p. 227—228° (Found: C, 67·2; H, 5·4; N, 17·6. $C_{18}H_{18}O_2N_4$ requires C, 67·1; H, 5·6; N, 17·4%).

The following were prepared from 1-*p*-aminophenylbenzotriazole as for the isomers just described: 1-p-(1-*cyano*cyclo*pentylamino*)*phenylbenzotriazole* (yield, 70%; reaction time, 15 hours), pale brown prisms, m. p. 165° (from ethanol; prolonged boiling with the solvent regenerated the original amine) (Found: C, 71·6; H, 6·1%), 1-p-(1-*carbamyl*cyclo*pentylamino*)-*phenylbenzotriazole* (yield almost quantitative), colourless needles, m. p. 204° (from aqueous ethanol) (Found: C, 67·2; H, 5·9%), and 1-p-(1-*carboxy*cyclo*pentylamino*)*phenylbenzotriazole* (yield almost quantitative; reaction time, 1 hour), practically colourless prisms, m. p. 232—233° (decomp.) (from aqueous ethanol) (Found: C, 66·9; H, 5·7%).

1′-*Phenyltriazolo*(5′ : 4′-3 : 4)*carbazole* (X; R = H).—A mixture of 5-amino-1-phenylbenzotriazole (12 g.) and 2-chloro*cyclo*hexanone (3·8 g.) was rapidly heated to 160°, and, after the vigorous reaction had subsided, the whole was cooled a little and extracted with hot dilute hydrochloric acid. Original amine (4·5 g.) was recovered from the extract, while the residue gave 5 : 6 : 7 : 8-*tetrahydro*-1′-*phenyltriazolo*(5′ : 4′-3 : 4)*carbazole* (5·1 g.) in colourless prisms, m. p. 222°, on crystallisation from aqueous ethanol (Found: C, 75·0; H, 5·6. $C_{18}H_{16}N_4$ requires C, 75·0; H, 5·6%). A mixture of the tetrahydro-compound (5·1 g.), chloranil (8·7 g.), and xylene (170 c.c.) was refluxed for 24 hours, then filtered whilst hot, and the solid which separated on cooling extracted with aqueous sodium hydroxide. After the residual 1′-*phenyl*-

triazolo(5′ : 4′-3 : 4)*carbazole* (2 g.) had been purified by adsorption from benzene on alumina, it crystallised from benzene in colourless plates, m. p. 252° (Found: C, 76·2; H, 4·6. $C_{18}H_{12}N_4$ requires C, 76·1; H, 4·2%).

5-N-*Nitrosobenzylamino*-1-*phenylbenzotriazole and* 1-p-N-*Nitrosobenzylaminophenylbenzotriazole*.—5-Benzylideneamino-1-phenylbenzotriazole, prepared by heating 5-amino-1-phenylbenzotriazole (5 g.) with benzaldehyde (2·8 g.) on the steam-bath for ½ hour, crystallised from ethanol in colourless plates (5·4 g.), m. p. 139° [Fries (*Annalen*, 1927, **454**, 153) gives m. p. 137°] (Found: C, 76·2; H, 4·6. Calc. for $C_{19}H_{14}N_4$: C, 76·5; H, 4·7%). After this compound (5·4 g.) in dioxan (120 c.c.) had been shaken for 2 hours with hydrogen in the presence of palladium–strontium carbonate at atmospheric temperature and pressure, and the solution filtered, removal of the solvent left 5-*benzylamino*-1-*phenylbenzotriazole* (5·4 g.), colourless needles, m. p. 111° (from aqueous ethanol) (Found: C, 75·8; H, 5·0. $C_{19}H_{16}N_4$ requires C, 76·0; H, 5·3%). Addition of a slight excess of aqueous sodium nitrite to the benzylamino-compound (5·4 g.) in acetic acid (70 c.c.) in the cold, and dilution with water, precipitated 5-N-*nitrosobenzylamino*-1-*phenylbenzotriazole* (5·4 g.), colourless prisms, m. p. 141° (from ethanol) (Found: C, 69·4; H, 4·8. $C_{19}H_{15}ON_5$ requires C, 69·3; H, 4·6%).

The following were prepared similarly from 1-*p*-aminophenylbenzotriazole: 1-p-*benzylideneaminophenylbenzotriazole* (yield, 75%), pale brown prisms, m. p. 143—145° (from ethanol) (Found: C, 76·9; H, 5·1%); 1-*p*-benzylaminophenylbenzotriazole (almost quantitative yield), a viscous syrup, which gave a *hydrochloride*, colourless plates, m. p. 223° (from ethanol–dilute hydrochloric acid) (Found: C, 67·8; H, 5·3. $C_{19}H_{17}N_4Cl$ requires C, 67·8; H, 5·1%); and 1-p-N-*nitrosobenzylaminophenylbenzotriazole* (yield, 80%), pale yellow needles, m. p. 155° (from ethanol) (Found: C, 69·4; H, 4·4%).

9-*Benzyl*-5 : 6 : 7 : 8-*tetrahydro*-1′-*phenyltriazolo*(5′ : 4′-3 : 4)*carbazole* (III; R = Ph·CH_2).—Zinc dust (6·8 g.) was gradually added during ¼ hour, with stirring, to a suspension of 5-*N*-nitrosobenzylamino-1-phenylbenzotriazole (4 g.) in a mixture of acetic acid (40 c.c.), water (12 c.c.), and *cyclo*hexanone (4 c.c.) at 55°. When the temperature was then slowly raised to 90° and kept there for 5 minutes, 9-*benzyl*-5 : 6 : 7 : 8-*tetrahydro*-1′-*phenyltriazolo*(5′ : 4′-3 : 4)*carbazole*, colourless needles (2·2 g.), m. p. 172° (from amyl alcohol), separated (Found: C, 79·2; H, 5·7. $C_{25}H_{22}N_4$ requires C, 79·4; H, 5·8%).

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84. *Synthesis of* 4-*Deoxy*-L-*ribose from* D-*Lyxose.*

By P. W. KENT and P. F. V. WARD.

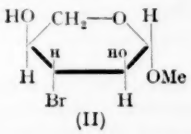
2 : 3-*iso*Propylidene α-methyl-D-lyxoside furnished a crystalline 4-toluene-*p*-sulphonate. After removal of the *iso*propylidene group, treatment of the product in alkaline conditions gave α-methyl-3 : 4-anhydro-D-lyxoside from which 4-bromo-4-deoxy-α-methyl-D-lyxoside was obtained. Hydrogenation of the bromo-compound gave β-methyl-4-deoxy-L-riboside. Neither this glycoside nor the corresponding free deoxy-sugar gave a positive Dische reaction.

THE principal known deoxyriboses are 2-deoxy- (Deriaz, Overend, Stacey, Teece, and Wiggins, *J.*, 1949, 1879), 3-deoxy- (Kent, Stacey, and Wiggins, *J.*, 1949, 1232), and 2 : 3-dideoxy-compounds (Allerton, Overend, and Stacey, *J.*, 1952, 255). We now report the synthesis of 4-deoxy-L-ribose.

Yields of deoxypentoses are, in general, poor by the arabinal method (cf. Meisenheimer and Jung, *Ber.*, 1927, **60**, 1462; Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836). Methods depending on the cleavage of an ethylene oxide ring have been used by Kent, Stacey, and Wiggins (*loc. cit.*), Mukherjee and Todd (*J.*, 1947, 969), and Prins (*J. Amer. Chem. Soc.*, 1948, **70**, 3955).

α-Methyl-D-lyxoside, formed by the action of methanolic hydrogen chloride on D-lyxose (Phelps and Hudson, *J. Amer. Chem. Soc.*, 1926, **48**, 503), gave a 2 : 3-*iso*propylidene compound which readily yielded crystalline 2 : 3-*iso*propylidene 4-toluene-*p*-sulphonyl α-methyl-D-lyxoside. Hydrolysis by dilute acetic acid furnished 4-toluene-*p*-sulphonyl α-methyl-D-lyxoside, whence the anhydro-sugar (I) was obtained by sodium methoxide at

room temperature. Scission of the anhydro-ring with hydrobromic acid gave a single bromo-sugar, which differed from the known 3-bromo-3-deoxy-β-methyl-L-xyloside (II) and was shown by its ready oxidation with lead tetra-acetate under the conditions described by Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) to be 4-bromo-4-deoxy-α-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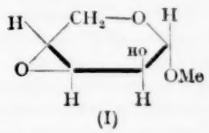
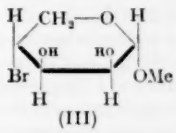

(I)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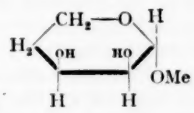
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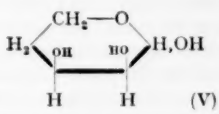
(V)

methyl-D-lyxoside (III). Catalytic hydrogenation then gave a deoxy-glycoside (IV), hydrolysed by acid to 4-deoxy-L-ribose (V), which was characterised as the crystalline *N'*-benzyl-*N'*-phenylhydrazone.

Although the Dische diphenylamine test (*Mikrochem.*, 1930, **8**, 4) is not completely specific to 2-deoxy-sugars (Allerton *et al.*, *loc. cit.*), neither 4-deoxyribose nor its methyl glycoside gives a positive result when heated with the reagent for 3·25 minutes at 100° (cf. Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222).

On paper chromatography with a butanol–ethanol–water system (Hirst, Hough, and Jones, *J.*, 1949, 928), 3-deoxyribose moved somewhat faster than 2- or 4-deoxyribose, although all had similar R_G values in these solvents.

The configurational designation D or L of 4-deoxyribose depends on the configuration of $C_{(3)}$, since $C_{(4)}$ and $C_{(5)}$ are both symmetrical. Hydrogenation of 4-bromo-4-deoxy-α-methyl-D-lyxoside yields, consequently, 4-deoxy-β-methyl-L-riboside.

Experimental

α-*Methyl*-D-*lyxoside*.—D-Lyxose (5 g.) was refluxed for 5 hours with 0·5% methanolic hydrogen chloride (100 c.c.). The solution was neutralised by dry silver carbonate and evaporated *in vacuo*. α-Methyl-D-lyxoside crystallised and, recrystallised from ethyl acetate (yield, 4 g.), had m. p. 108—109°, $[\alpha]_D^{22}$ +51·8° (*c*, 0·6 in H_2O) (Found: OMe, 18·4. Calc. for $C_6H_{12}O_5$: OMe, 18·9%).

2 : 3-iso*Propylidene* α-*Methyl*-D-*lyxoside*.—The foregoing glycoside (3 g.) was shaken at room temperature with dry acetone (50 c.c.) and concentrated sulphuric acid (0·5 c.c.) for 24 hours. The acid was neutralised with anhydrous sodium carbonate and, after removal of the solvent, the syrupy product was distilled with a trace of barium carbonate in a high vacuum. It had m. p. 40—41°, b. p. 65°/0·02 mm., n_D^{23} 1·4575, $[\alpha]_D^{22}$ +42·7° (*c*, 0·8 in EtOH) (yield 2·8 g.) (Found: C, 53·5; H, 7·8; OMe, 15·0. Calc. for $C_9H_{16}O_5$: C, 53·5; H, 7·85; OMe, 15·2%).

2 : 3-iso*Propylidene* 4-*Toluene*-p-*sulphonyl* α-*Methyl*-D-*lyxoside*.—The above *iso*propylidene derivative (1·5 g.) in pyridine (10 c.c.) at 0° was treated with toluene-*p*-sulphonyl chloride (4 g.), After 24 hours at room temperature, pouring the solution into cold water and recrystallisation from ethanol gave the *ester*, m. p. 96—97°, $[\alpha]_D^{22}$ −10·2° (*c*, 1·85 in EtOH) (Found: C, 53·5; H, 6·1; S, 8·0. $C_{16}H_{22}O_7S$ requires C, 53·5; H, 6·15; S, 8·95%).

4-*Toluene*-p-*sulphonyl* α-*Methyl*-D-*lyxoside*.—The previous compound (1·15 g.) was warmed at 90—100° for 3 hours with 0·1% acetic acid (25 c.c.), then evaporated in a vacuum-desiccator (KOH). The *product*, which did not crystallise, had n_D^{21} 1·5240, $[\alpha]_D^{21}$ +30° (*c*, 1·4 in $CHCl_3$) (Found: OMe, 9·8. $C_{13}H_{18}O_7S$ requires OMe, 9·8%).

α-*Methyl*-3 : 4-*anhydro*-D-*lyoxide* (I).—4-Toluene-*p*-sulphonyl α-methyl-D-lyxoside (0·4 g.) in chloroform (10 c.c.) at 0° was treated with sodium methoxide in methanol (2 g. of sodium and 50 c.c. of methanol). After 12 hours at room temperature, the solution was diluted with chloroform (50 c.c.) and shaken with water (100 c.c.). The aqueous layer was neutralised with dilute sulphuric acid, and evaporated to dryness. The residue was extracted repeatedly with hot ethyl acetate, and the extract evaporated to dryness. The product distilled at 115° (bath-temp.)/0·02 mm. and became semicrystalline. The *anhydro*-compound had $[\alpha]_D^{22}$ +98·6° (*c*, 1·4 in $COMe_2$), n_D^{22} 1·4350 (Found: OMe, 21·25. $C_6H_{10}O_4$ requires OMe, 21·4%).

Scission of α-*Methyl*-3 : 4-*anhydro*-D-*lyxoside with Hydrobromic Acid*.—The anhydro-glycoside (I) (0·2 g.) was heated in acetone (50 c.c.) containing 2·04N-hydrobromic acid (5 c.c.) under reflux for 5 hours. The solution was neutralised by addition of lead carbonate and the filtrate concentrated to a small volume. The solid 4-*bromo*-4-*deoxy*-α-*methyl*-D-*lyxoside* (III) (0·1 g.), which separated, was recrystallised twice from ethyl acetate and had m. p. 134—135°, $[\alpha]_D^{21}$ +14·6° (*c*, 0·7 in MeOH) (Found : Br, 33·3. $C_6H_{11}O_4Br$ requires Br, 35·2%). 3-Bromo-3-deoxy-β-methyl-D-xyloside has m. p. 101—102° $[\alpha]_D^{14}$ −16·4° (*c*, 0·4 in MeOH).

No evidence was obtained of another bromo-compound.

Oxidation of 4-*Bromo*-4-*deoxy*-α-*methyl*-D-*lyxoside with Lead Tetra-acetate*.—The rate of oxidation of the bromo-compound with lead tetra-acetate in acetic acid was compared with that of α-methyl-mannoside and -glucoside under the conditions recorded by Hockett and McClenahan (*loc. cit.*) in darkness. To about 10 mg. of the glycoside in acetic acid (12 c.c.) were added 12·5 c.c. of a standard solution of lead tetra-acetate (approx. 30 g./l. in acetic acid). The final volume was made up to 25·0 c.c. with acetic acid. At intervals, 5-c.c. portions were removed and transferred immediately into 10 c.c. of aqueous potassium iodide containing a little potassium sulphate. The iodine liberated was titrated with 0·02N-sodium thiosulphate. A control test was carried out on 12·5 c.c. of the lead tetra-acetate solution diluted to 25 c.c. with " AnalaR " acetic acid. The following results were obtained (corrected for control) :

Bromo-pentoside				
Time (hr.)	0·33	3	6	20
$Pb(OAc)_4$ consumed (mole/mole)	0·0031	0·031	0·048	0·106
α-*Methylmannoside*				
Time (hr.)	0·33	3	6	20
$Pb(OAc)_4$ consumed (mole/mole)	0·0052	0·030	0·054	0·099
α-*Methylglucoside*				
Time (hr.)	0·33	3	6	20
$Pb(OAc)_4$ consumed (mole/mole)	0·0006	0·006	0·012	0·026

Hydrogenolysis of 4-*Bromo*-4-deoxy-α-*methyl*-D-*lyxoside* (III).—A methanolic solution (30 c.c.) of the bromo-sugar (III) (0·2 g.) was shaken at room temperature in hydrogen, in the presence of freshly prepared Raney nickel (*ca.* 1 g.) and calcium hydroxide (0·1 g.). After 8 hours, the solution gave positive tests for bromide and was saturated with carbon dioxide and filtered. The filtrate was evaporated to dryness and the residue extracted exhaustively with hot ethyl acetate. Concentration of this extract yielded β-*methyl*-4-*deoxy*-L-*riboside* (IV) (0·12 g.), $[\alpha]_D^{21}$ +39·2° (*c*, 0·2 in H_2O), n_D^{21} 1·4815 (Found : OMe, 20·5. $C_6H_{12}O_4$ requires OMe, 21·0%).

4-*Deoxy*-L-*ribose* (V).—β-Methyl-4-deoxy-L-riboside (IV) (0·1 g.) was hydrolysed at 100° with N-sulphuric acid (20 c.c.). In 4 hours the optical rotation changed from +39° to +23° (const.). The solution was neutralised (phenolphthalein) with sodium carbonate, then evaporated to dryness, and the residue extracted with hot ethyl acetate. Evaporation of the extract gave 4-deoxy-L-ribose (V) (0·06 g.), which reduced Fehling's solution readily and had n_D^{22} 1·4920, $[\alpha]_D^{21}$ +23·1° (*c*, 0·2 in H_2O).

In 75% aqueous ethanol at 70° (1 hour) this gave a *benzylphenylhydrazone*, m. p. 102—103° (from aqueous ethanol) (Found : N, 8·3. $C_{18}H_{22}O_3N_2$ requires N, 8·9%).

Dische Tests.—The reagent was prepared from pure diphenylamine (2 g.) (twice recrystallised from ligroin) (Dische, *loc. cit.*). The test was carried out simultaneously on D-ribose (1·6 mg.) 2-deoxy-L-ribose (1·93 mg.), 3-deoxy-D-ribose (1·1 mg.), and 4-deoxy-L-ribose (1·2 mg.), each in water (2 c.c.) containing the reagent (4 c.c.). The solutions, and a control consisting of water (2 c.c.) and reagent (4 c.c.) alone, were heated in a boiling-water bath for 3·25 minutes, then cooled in ice for 15 minutes. The intensities of the colours were measured on a Spekker photo-electric colorimeter with Ilford filter 606. The following molecular extinction coefficients were obtained : D-ribose, 0; 2-deoxy-L-ribose, 2720; 3-deoxy-D-ribose, 146; 4-deoxy-L-ribose, 0.

Chromatography of 2-, 3-, *and* 4-*Deoxyribose*.—With butanol–ethanol–water (4 : 1 : 5) and Whatman No. 1 filter paper, as described by Hirst *et al.* (*loc. cit.*), the following R_G values were determined at 20° (bands were observed after spraying with aniline hydrogen phthalate) : D-ribose, 0·34, 2-, 0·50, 3-, 0·60, and 4-deoxyribose, 0·53.

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85. *Anionotropic Systems. Part I.* The Effect of a Nitro-substituent on Equilibrium and Mobility in the 1 : 3-Diphenylallyl Alcohol System.*

By E. A. Braude and E. S. Waight.

Rate and equilibrium constants have been determined for the interconversion of 3-*p*-nitrophenyl-1-phenyl- (III) and 1-*p*-nitrophenyl-3-phenyl-allyl alcohol (IV) under the influence of hydrochloric acid in aqueous dioxan. The equilibrium mixture contains 55% of (III) and 45% of (IV); the equilibrium constant ($K = 0{\cdot}83 \pm 0{\cdot}01$) varies less than the experimental error over the temperature range 30—80°. The free-energy change ($\Delta G = 0{\cdot}12$ kcal./mole), representing the difference between the conjugation energies of an ethylenic bond with a phenyl and a *p*-nitrophenyl group, is unexpectedly small.

The rate and activation energy of the rearrangement of (III) are very similar to those of 1-phenylallyl alcohol (V), showing that the effect of the *p*-nitrophenyl group on mobility is practically nil. This indicates that the deactivating, electron-attractive influence of the nitro-substituent is compensated by an electromeric effect of the phenyl ring in the opposite direction.

Hitherto, quantitative studies on three-carbon anionotropic systems of the type (I) $\rightleftharpoons$ (II) have mainly been concerned with examples in which X is a strongly conjugating group (*e.g.*, C:C, C:C, Ph, etc.) and Y is a weakly conjugating group (*e.g.*, H, Me, etc.), and in which the equilibrium consequently lies far on the side of the more highly conjugated isomer (II). As has been shown previously, such systems provide an excellent basis for investigating the electronic properties of substituents by means of rate measurements, but the equilibrium constants are too large to be determined. Added interest, therefore, attaches to examples in which X and Y have sufficiently similar conjugating properties to render the equilibrium measurable. The free-energy change of the reaction (I) $\rightleftharpoons$ (II)

(I) A·CHX·CH:CHY $\rightleftharpoons$ CHX:CH·CHYA (II)

will correspond closely to the difference in resonance energies of X·C:C and Y·C:C, thus providing a kinetic method of determining such quantities. This method is capable of greater precision than is attainable in the evaluation of resonance energies from thermochemical data, particularly when small differences are involved, and is less subject to uncertainties of interpretation. The only assumption which has to be made is the very reasonable one that any stabilisation due to hyperconjugation of the C–A bond will be the same in (I) and (II).

We now report the results for a model system, the reversible isomerisation of (III) and (IV). This was chosen because the nitro-group is one of the most strongly polar of common substituents; if the equilibrium point is suitable in this case, as it has been found to be, a wide applicability for the method is assured.

(III) Ph·CH(OH)·CH:CH·C_6H_4·NO_2 $\rightleftharpoons$ Ph·CH:CH·CH(OH)·C_6H_4·NO_2 (IV)

The two alcohols were conveniently prepared in good yields by Ponndorf reduction of the corresponding ketones, as crystalline solids of almost identical, but mutually depressed, melting points, and each formed its own *p*-nitrobenzoate under appropriate conditions. The two alcohols are characterised by distinct ultra-violet light absorption properties (see Figure); (III) exhibits an intense band at 3110 Å associated with the *p*-nitrostyryl chromophore (cf. Pestemer, Langer, and Manchen, *Monatsh.*, 1936, **68**, 326), while (IV) exhibits a wide band with a maximum at 2515 Å arising from superposition of the absorption due to the nitrophenyl and the styryl chromophore. Mixtures of (III) and (IV) are readily analysed by this means, and it is found that, under the influence of acids, both alcohols isomerise to give the same equilibrium mixture containing about 55% of (III) and 45% of (IV). The composition of the equilibrium mixture is scarcely affected by the experi-

* Continuation of two separate series [" Studies on Molecular Rearrangement " Part IX, *J.*, 1952, 4155) and " The Kinetics of Anionotropic Rearrangement " (Part X, *J.*, 1952, 4158)] which will now be merged.

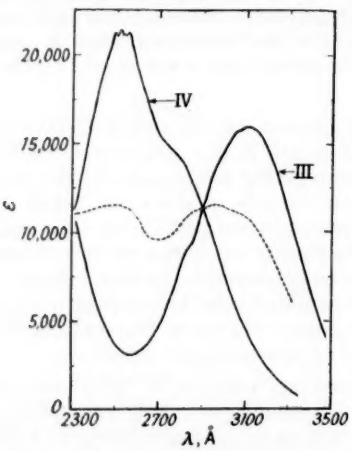
mental conditions (*e.g.*, solvent, temperature, and catalyst concentration), but no interconversion takes place in the absence of acid catalyst under the conditions examined.

A quantitative spectrometric investigation of the system (III)–(IV) was carried out in 60% aqueous dioxan–0·1M-hydrochloric acid. The reactions exhibit normal first-order kinetics; first-order rate constants and equilibrium constants are given in Table 1. The

TABLE 1. *First-order rate constants (in min.$^{-1}$) and equilibrium constants for the system* (III) $\underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}}$ (IV) *in 60% aqueous dioxan–0·1M-hydrochloric acid:* $k = k_1 + k_{-1}$; $K = k_1/k_{-1}$.

Temp.	K	10^4k	10^4k_{-1}	10^4k_1	Temp.	K	10^4k	10^4k_{-1}	10^4k_1
30°	0·83	10·2	5·6	4·6	60°	0·83	322	176	146
40	0·82	36·6	20·2	16·4	70	0·84	950	516	434
50	0·83	103	56	47	80	0·83	2370	1300	1070

equilibrium constant, $K = 0·83$, changes by less than 2% over the temperature range 30—80°. The derived value for the free-energy change is $\Delta G = 0·12$ kcal./mole; the



Ultra-violet light absorption of (III), (IV), *and their equilibrium mixture* (*broken curve*) *in ethanol solution.*

enthalpy change ΔH must be of the same order or smaller, and the entropy change ΔS must be less than 0·5 cal. mole^{-1} deg.$^{-1}$.

It is instructive to compare the system (III) $\rightleftharpoons$ (IV) with, on the one hand, the irreversible rearrangement of 1-phenylallyl alcohol (V) to cinnamyl alcohol (VI) (Braude,

(V) HO·CHPh·CH:CH_2 $\rightleftharpoons$ CHPh:CH·CH_2·OH (VI)

Jones, and Stern, *J.*, 1946, 396) and, on the other, with the symmetrical system, 1 : 3-diphenylallyl alcohol (VII), in which the two isomers are identical and the equilibrium constant has the value $K = 1$.

(VII) HO·CHPh·CH:CHPh $\rightleftharpoons$ CHPh:CH·CHPh·OH

The reaction rate in the latter case obviously cannot be determined directly, but it can be accurately extrapolated from measurements (to be published) by Mr. P. H. Gore on analogues in which one of the phenyl groups is replaced by a naphthyl group, in conjunction with data previously obtained for 1-aryl-3-methylallyl alcohols (Braude and Fawcett, *J.*, 1950, 800). Comparison of the data (Table 2) for (III) and (V) shows that a *p*-nitrophenyl group has a large effect on equilibrium, but only a negligible effect on mobility, the rate constants and energies of activation being very similar. By contrast, comparison of the data for (III) and (VII) shows that a *p*-nitro-substituent has a small effect on equilibrium, but a large effect on mobility, decreasing the rate constant by a factor of *ca.* 200 and increasing the energy of activation by *ca.* 2 kcal./mole.

The large effect of the *p*-nitrophenyl group on equilibrium is to be expected, since the conjugating properties of such a group will be very different from that of a hydrogen atom. Similarly, the large effect of the *p*-nitro-substituent on mobility is also as expected, for it

TABLE 2. *Effects of substituents in the rearrangement*

$$HO{\cdot}CHPh{\cdot}CH{:}CHX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CHPh{:}CH{\cdot}CHX{\cdot}OH.$$

X	K	$-\Delta G_{30°}$ (kcal./mole)	k'_1 (min.$^{-1}$) *	$E_{Arr.}$ (kcal./mole)	$\log_{10} A$ †
H (V) ‡	>10	>2	0·0038	24·5	14·6
Ph (VII) §	1	0	0·70	21·5	14·7
$C_6H_4{\cdot}NO_2$ (III)	0·83	−0·12	0·0046	23·7	14·1

* Specific rate constant (k_1/acid concentration) at 30° for 60% aqueous dioxan–hydrochloric acid.

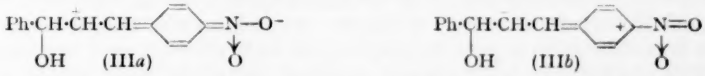
† Defined by $\log k'$ (sec.$^{-1}$) $= Ae^{-E_{Arr.}/RT}$.

‡ Part V, *J.*, 1946, 396. The value for the activation energy is a revised one, based on new measurements.

§ Extrapolated values based on unpublished measurements by Mr. P. H. Gore.

is known that anionotropic rearrangements are very sensitive to electronic influences, being strongly facilitated by electron-donating, and strongly retarded by electron-attracting substituents (Braude, *Quart. Reviews*, 1950, **4**, 404).

On the other hand, the effects of the *p*-nitro-substituent on equilibrium and of a *p*-nitrophenyl group on mobility are unexpectedly small, obviously owing to some common factor which causes the mobilities (k_1 and k_{-1}) of both (III) and (IV) to differ little from that of (V), and hence the ratio k_1/k_{-1} to differ little from unity. The extra conjugation present in the nitrostyrene system of (III) evidently contributes only little resonance stabilisation additional to that of the styrene system (IV), and the retarding influence of the nitro-substituent must be compensated by an independent accelerating influence of the phenyl ring to which it is attached. It is as if the allyl grouping competes successfully with the nitro-substituent for the benzenoid π-electrons; in terms of the valency-bond representation of mesomeric electron displacements, we must conclude that contribution from structures of type (III*b*) can equal the combined effects of contributions of type (III*a*) and of the negative inductive effect of the nitro-substituent.



Very little information is available concerning the relative strength of conjugation of an ethylenic bond with a substituted and an unsubstituted phenyl group. Theoretically, one might expect a strongly polar substituent, independently of the sign of its mesomeric effect, to assist the π-electron interaction. This is borne out by the recent calculations by Pullmann (*Compt. rend.*, 1948, **226**, 486) and Coulson and Jacobs (*J.*, 1949, 1983) for *p*-aminostilbene, which indicate that the aminophenyl group interacts more strongly than the unsubstituted phenyl group with the central ethylenic link. The difference between the conjugation energies of an ethylenic bond with an aminophenyl and a phenyl group can be estimated from Coulson and Jacobs's results as *ca.* 300 cal.* This is of the same order as, but somewhat larger than, the value of 120 cal. obtained here for the difference between the conjugation energies of an ethylenic bond with a nitrophenyl and a phenyl group.

$$(VIII)\quad HO{\cdot}CHPh{\cdot}CH{:}CH{\cdot}C_6H_4Cl\text{-}p \rightleftharpoons CHPh{:}CH{\cdot}CH(OH){\cdot}C_6H_4Cl\text{-}p \quad (IX)$$

$$(X)\quad Ph{\cdot}CH_2{\cdot}N{:}CH{\cdot}C_6H_4{\cdot}NO_2\text{-}m \rightleftharpoons Ph{\cdot}CH{:}N{\cdot}CH_2{\cdot}C_6H_4{\cdot}NO_2\text{-}m \quad (XI)$$

Empirically, the nearest analogies come from Burton and Ingold's work (*J.*, 1928, 904) on the 3-*p*-chlorophenyl-1-phenylallyl alcohol system (VIII) ⇌ (IX) and from Shoppee's work (*J.*, 1932, 696) on the reversible prototropic isomerisation of the azomethines (X) and (XI). Burton and Ingold did not make quantitative measurements, but concluded

* This estimate has been obtained as follows. According to Coulson and Jacobs, the charge migration in aniline confers a charge of 0·090*e* on the nitrogen atom; this is associated with a resonance energy of *ca.* 5000 cal. (Wheland, "The Theory of Resonance," Wiley, New York, 1944). In 4-aminostilbene, the charge on the nitrogen atom is increased to 0·096*e*; the difference of 0·006*e* will be approximately equivalent to an additional stabilisation of 5000 × 6/90 = 300 cal. We are indebted to Professor C. A. Coulson, F.R.S., for pointing out to us that this estimate does not take explicit account of the change in bond orders with substitution, but that the bond-order energy term is likely to be small compared with the Coulomb energy term.

from qualitative evidence that (VIII) " is the main isomeride; " if this is correct, the much more strongly polar *p*-nitro-substituent might be expected to result in a considerably larger displacement of the equilibrium. In the prototropic system studied by Shoppee, the equilibrium mixture was found to contain 68% of (X) at 82°; again, a *p*-nitro-substituent might be expected to have an even larger effect. However, the direct comparison between the anionotropic and prototropic systems is not necessarily valid; in the former, the entities actually undergoing equilibrium are the oxonium ions formed by addition of a proton to a hydroxyl group and in which the positive charge will have little influence on the conjugated system, whereas in prototropy the entities undergoing equilibration are probably the mesomeric carbanions formed by loss of a proton from the methylene group and in which the negative charge forms an integral part of the conjugated system (cf. Braude and Forbes, *J.*, 1951, 1755).

We now turn to the effect of the *p*-nitrophenyl group on mobility and to the opposing electronic influences of the phenyl group and the nitro-substituent which it indicates. It is well known that an unsubstituted phenyl group can exert an electron-donating or electron-attracting influence by the electromeric mechanism according to the demands of the reaction, and the accelerating effect of phenyl on anionotropy is shown by comparing the data for (V) and (III); but, in the presence of a strongly polar nuclear substituent, it is usual for the substituent to take control even when it hinders the reaction. The situation is reminiscent of that encountered in the electrophilic substitution of *p*-nitrodiphenyl and β-nitrocinnamic acid, in which the *p*-nitrophenyl and β-nitrovinyl groups cause overall deactivation coupled with *op*-direction (cf. Gull and Turner, *J.*, 1929, 491; Hartman and Robertson, *J.*, 1945, 891; Bordwell and Rohde, *J. Amer. Chem. Soc.*, 1948, **70**, 1191). This has also been ascribed to the $+T$ effects of the phenyl and vinyl groups acting in opposition to the $-I,-T$ effects of the nitro-substituent. Unlike the present case, however, the activating effect of the phenyl ring is heavily outweighed by the deactivating effect of the nitro-substituent; thus the rates of nuclear halogenation of the *p*-nitrophenyl derivatives are decreased by factors of *ca.* 10^2 with respect to the unsubstituted compounds (Hartman and Robertson, *loc. cit.*). Similarly, the electrophilic addition of halogens to acrylic acid is facilitated by a phenyl group but strongly retarded by a nitrophenyl group (relative rates of chlorine addition under standard conditions are: acrylic acid 0·018, cinnamic acid 4·9, methyl *p*-nitrocinnamate 0·0011; cf. de la Mare, *Quart. Reviews*, 1949, **3**, 126). The most probable reason for the difference between the effects of a *p*-nitrophenyl group on the rates of acid-catalysed anionotropy and of electrophilic halogenation is that the former involves initial attack by a positively charged ion (H^+),* whereas the latter involves attack by an essentially neutral reagent (Cl_2, Br_2): the ion will be much more effective than a neutral molecule in bringing into play the compensating $+T$ effect of the phenyl ring.

Experimental

(M. p.s are uncorrected. Light-absorption data were determined on a Hilger Spekker photographic instrument except where otherwise stated.)

3-p-*Nitrophenyl*-1-*phenylallyl Alcohol* (III).—*p*-Nitrobenzaldehyde (25 g.) was condensed with acetophenone (20 g.) in the presence of methanolic potassium hydroxide (5%; 125 ml.) at room temperature, giving *p*-nitrostyryl phenyl ketone (38 g., 90%), m. p. 163° (cf. Sorge, *Ber.*, 1902, **35**, 1068; Wieland, *ibid.*, 1904, **37**, 1149). The ketone (5 g.), aluminium *iso*propoxide (32 g.), *iso*propanol (30 ml.), and benzene (120 ml.) were heated under partial reflux until formation of acetone ceased (about 4 hours). After cooling, excess of 2N-sodium hydroxide was added, the benzene layer separated, and the aqueous layer extracted with benzene. Evaporation of the combined benzene solutions afforded 3-p-*nitrophenyl*-1-*phenylallyl alcohol* (4·2 g., 84%), which crystallised from benzene–light petroleum (b. p. 60—80°) in pale yellow plates, m. p. 84—85° (Found: C, 70·2; H, 5·4; N, 5·5. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%). Light absorption in ethanol: $\lambda_{max.}$ 3110 Å; ε 16,450 (cf. Fig.). The p-*nitrobenzoate*, obtained from the alcohol and *p*-nitrobenzoyl chloride in dry pyridine at 0°, separated from methanol–ethyl

* The addition of the proton to the hydroxyl group is, of course, reversible and not rate-determining, but the equilibrium concentration of the oxonium ion enters the rate equation (cf. Braude, *J.*, 1948, 794).

acetate–water as almost colourless crystals, m. p. 135—136° (Found: C, 64·9; H, 4·3; N, 7·0. $C_{22}H_{16}O_6N_2$ requires C, 65·3; H, 4·0; N, 6·9%). Light absorption in chloroform: $\lambda_{max.}$ 2570, 2680, 2800, and 3040 Å; ε 18,000, 18,000, 18,000, and 22,000, respectively.

1-p-*Nitrophenyl*-3-*phenylallyl Alcohol* (IV).—*p*-Nitroacetophenone (25 g.; Walker and Hauser, *J. Amer. Chem. Soc.*, **1946**, **68**, 1368) and benzaldehyde (16 g.) in the presence of methanolic potassium hydroxide (5%, 125 ml.) gave *p*-nitrophenyl styryl ketone (25 g., 65%), m. p. 145° after recrystallisation from ethanol–benzene (cf. Weygand and Günther, *Annalen*, 1927, **459**, 115). Reduction of the ketone (5 g.) with aluminium *iso*propoxide (16 g.) and *iso*propanol (100 ml.) as above afforded 1-p-*nitrophenyl*-3-*phenylallyl alcohol* (3·7 g., 74%), which crystallised from benzene–light petroleum (b. p. 60—80°) as plates, m. p. 83—84°, depressed on admixture with the isomer above (Found: C, 70·6; H, 5·1; N, 5·4%). Light absorption in ethanol: $\lambda_{max.}$ 2515 and 2800 Å; ε 21,300 and 12,700 (cf. Fig.). The p-*nitrobenzoate*, crystallised from methanol–ethyl acetate–water, had m. p. 151° (Found: C, 65·4; H, 4·2; N, 7·2%; *M*, in camphor, 395. $C_{22}H_{16}O_6N_2$ requires C, 65·3; H, 4·0; N, 6·9%; *M*, 404). Light absorption in chloroform: $\lambda_{max.}$ 2590 and 2660 Å; ε 40,000 and 36,000.

Interconversion of the Two Alcohols.—A solution of the alcohol (III) (1 g.) in 0·1M-hydrochloric acid–60% aqueous dioxan (100 ml.) was kept at 78° for 1 hour, then neutralised by potassium carbonate, and most of the solvent removed at 0·1 mm. The residue was diluted with water and extracted with ether, and the extract dried (Na_2SO_4) and evaporated under reduced pressure. The oily residue (0·95 g.) solidified when stirred under light petroleum (b. p. 40—60°) and then had m. p. 61—71°. The light absorption of this product corresponded to that of a mixture of 55% of (III) and 45% of (IV). An artificial mixture of the two alcohols in these proportions had m. p. 61—71°, unaltered on admixture with the rearrangement product. A similar experiment with the alcohol (IV) gave an identical result.

Kinetic Measurements.—Weighed amounts of alcohol (approx. 20 mg.) were added to 25 ml. of reaction medium contained in a reaction vessel of the type previously described (*J.*, 1946, 396), in a thermostat. 1-Ml. samples were withdrawn at appropriate intervals and added to 95% aqueous ethanol containing sufficient potassium hydroxide to neutralise the hydrochloric acid. The absorption intensities at the maxima of the two isomers were determined by using a Beckman photoelectric spectrophotometer provided with special cells of 0·1-cm. thickness. The intensity values, expressed as $E^{1\%}_{1\,cm.}$, of the separate isomers are 139 at 2515 Å and 645 at 3110 Å for (III), and 842 at 2515 Å and 154 at 3110 Å for (IV). First-order rate constants for (III) were calculated from $k = (2{\cdot}3/t) \log_{10}[(a - 139)/(a - x)]$, where x is the intensity at time t and a the final intensity at 2515 Å, and those for (IV) were calculated from $k = (2{\cdot}3/t) \log_{10}[(b - 154)/(b - x)]$, where b is the final intensity at 3110 Å. Equilibrium constants were calculated from $K = [IV]/[III] = (a - 139)/(842 - a)$ and from $K = (645 - b)/(b - 154)$. The results obtained for the two isomers were in good agreement; four typical runs at the lowest and the highest temperature employed are reproduced below. The reaction medium was prepared by mixing 61 ml. of dioxan and 10 ml. of M-hydrochloric acid, and adding water to give a total volume of 100 ml.

(i) Rearrangement of (III) at 30°. Alcohol concn. 0·0030M.

Time (min.)	0	150	300	470	725	1345	3200
$E^{1\%}_{1\,cm.}$ (2515 Å)	139	184	224	257	303	375	458
$E^{1\%}_{1\,cm.}$ (3110 Å)	645	—	—	—	—	—	428
10^4k (min.$^{-1}$)	—	10·1	10·3	9·9	10·0	10·0	—

K (mean) = 0·82; k (mean) = 10·1, k_1 = 5·5, k_{-1} = 4·6.

(ii) Rearrangement of (IV) at 30°. Alcohol concn. 0·0028M.

Time (min.)	0	150	300	470	725	1345	3200
$E^{1\%}_{1\,cm.}$ (2515 Å)	842	—	—	—	—	—	459
$E^{1\%}_{1\,cm.}$ (3110 Å)	154	196	222	252	300	348	423
10^4k (min.$^{-1}$)	—	11·3	9·7	9·6	10·8	9·5	—

K (mean) = 0·83; k (mean) = 10·2, k_1 = 5·6, k_{-1} = 4·6.

(iii) Rearrangement of (III) at 80°. Alcohol concn. 0·0026M.

Time (min.)	0	1	2	3	4	5	110
$E^{1\%}_{1\,cm.}$ (2515 Å)	139	209	262	305	337	363	458
$E^{1\%}_{1\,cm.}$ (3110 Å)	645	—	—	—	—	—	426
10^4k (min.$^{-1}$)	—	2480	2440	2440	2420	2420	—

K (mean) = 0·82; k (mean) = 2440, k_1 = 1340, k_{-1} = 1100.

(iv) Rearrangement of (IV) at 80°. Alcohol concn. 0·0030M.

Time (min.)	0	1	2	3	4	5	110
$E^{1\%}_{1\,cm.}$ (2515 Å)	842	—	—	—	—	—	460
$E^{1\%}_{1\,cm.}$ (3110 Å)	154	211	253	289	315	336	424
10^4k (min.$^{-1}$)	—	2410	2280	2320	2270	2250	—

K (mean) = 0·83; k (mean) = 2310, k_1 = 1260, k_{-1} = 1050.

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86. *Steroidal Alkaloids. Part I. The Functional Groups of Cevine.*

By D. H. R. Barton and J. F. Eastham.

The steroidal tertiary alkamine, cevine, $C_{27}H_{43}O_8N$, contains a masked secondary α-ketol system, which also appears to be present in the related alkamines germine and protoverine. This system accounts for three of the oxygen atoms; three more are present as non-acylable tertiary hydroxyl groups and one as an easily acylated hydroxyl function; the remaining oxygen is accounted for as a difficultly acylated hydroxyl group.

Cevine and its derivatives have been examined for their susceptibility to glycol cleavage by periodic acid and lead tetra-acetate.

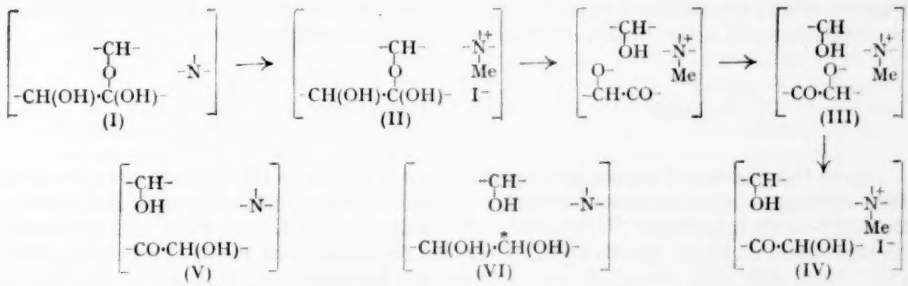
The steroidal alkamine cevine (see Fieser and Fieser, "Natural Products related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., p. 600 *et seq.*, and Henry, "The Plant Alkaloids," 4th Edn., J. and A. Churchill Ltd., p. 700 *et seq.*), has the molecular formula $C_{27}H_{43}O_8N$. A study of the far ultra-violet absorption spectrum (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737) reveals the absence of an ethylenic linkage, whilst the infra-red spectrum (Jaffé and Jacobs, *J. Biol. Chem.*, 1951, **193**, 325; Stoll and Seebeck, *Helv. Chim. Acta*, 1952, **35**, 1270) shows the absence of a carbonyl group. Cevine has all the properties of a tertiary amine; it gives a crystalline oxide with hydrogen peroxide (Freund, *Ber.*, 1904, **37**, 1946) and forms quaternary salts with ease. Further it is a moderately strong base ($pK_b = 4{\cdot}26$) (Jacobs and Craig, *J. Biol. Chem.*, 1938, **125**, 625; see also the Experimental section). In view of these facts cevine must be heptacyclic and not hexacyclic (cf. Fieser and Fieser, *op. cit.*).

Cevine readily forms diacyl derivatives, thus showing the presence of two primary or secondary hydroxyl groups. On reduction with sodium and butanol or (better) ethanol cevine affords dihydrocevine, whilst an isomeric dihydro-compound is formed on catalytic hydrogenation in the presence of Raney nickel (Jacobs and Craig, *loc. cit.*). Cevine reduces ammoniacal silver nitrate in the cold and Fehling's solution on warming (Freund and Schwarz, *Ber.*, 1899, **32**, 800). It seemed to us, *ab origine*, that all these observations would be best explained if cevine were a masked secondary α-ketol containing the grouping (I). The alternative of a masked aldehyde function was dismissed on the grounds that cevine is stable to hot very concentrated sodium ethoxide (see Experimental). The conclusion was confirmed by the following experiments.

Freund and Schwarz (*J. pr. Chem.*, 1918, **96**, 237) and later Jacobs and Craig (*loc. cit.*) observed that when cevine methiodide was subjected to conditions suitable for Hofmann degradation, the reaction did not pursue the expected path, but that instead a betaine, $C_{28}H_{45}O_8N$, was formed. This betaine gives crystalline salts (Freund and Schwarz, *loc. cit.*) and we have shown specifically that the hydriodide, $C_{28}H_{46}O_8NI$, is not identical with cevine methiodide. We have found that both the betaine and its hydriodide contain carbonyl groups, for they show intense absorption maxima in the infra-red at 1710 cm.$^{-1}$, values

indicative of a ketone grouping contained in a six-membered ring. These results can be plausibly interpreted by the expressions (II) for cevine methiodide, (III) for the betaine, and (IV) for the derived hydriodide. Thus we formulate the betaine as a secondary α-ketolic betaine; the infra-red spectrum, of course, excludes the possibility (cf. Gäumann and Günthard, *Helv. Chim. Acta*, **1952**, **35**, 53) that it could be a carboxylate betaine. The function of the vigorous alkaline conditions in the preparation of the betaine is, therefore, to equilibrate the α-ketol grouping. The two dihydrocevines are to be formulated as stereoisomers at the secondary carbon atom marked with the asterisk in (VI). The one formed under alkaline conditions will have the equatorial hydroxyl, that obtained by hydrogenation the polar hydroxyl group.

Further evidence in support of the masked α-ketol formula for cevine comes from two directions. First, cevine is weakly acidic, forming a crystalline potassium derivative (Hess and Mohr, *Ber.*, **1919**, **52**, 1984), advantage of which is taken in the isolation of cevine (cf. Macbeth and Robinson, *J.*, **1922**, **121**, 1571). Secondly, the elegant work of Stoll and Seebeck (*loc. cit.*) has led to the important discovery that cevine is *not* the parent alkamine of the ester alkaloids present in the " veratrine alkaloids." The Swiss authors have shown that cevadine and veratridine, previously regarded as ester alkaloids derived from cevine, in fact, give rise on mild alkaline hydrolysis to an isomeric steroidal alkamine cevagenin. The latter is readily isomerised to cevine by strong potassium hydroxide. Cevagenin is a ketone as shown by the infra-red carbonyl frequency at 1707 cm.$^{-1}$ identical in position with that of the betaine and its hydriodide (see above). It must be given the partial formula (V). Cevagenin affords a crystalline oxime under neutral conditions whereas cevine does not.



We believe that the steroidal alkaloid germine, $C_{27}H_{43}O_8N$, which is similar to cevine in many respects (Fieser and Fieser, *op. cit.*), also contains a masked α-ketol system. This is consistent with the isomerisation of germine by alkali to *iso*germine which, unlike germine, contains a carbonyl group (Fried, Numerof, and Coy, *J. Amer. Chem. Soc.*, **1952**, **74**, 3041) and affords an oxime (Jaffé and Jacobs, *loc. cit.*). No doubt the relation between protoverine and *iso*protoverine (Jacobs and Craig, *J. Biol. Chem.*, **1943**, **149**, 271) is the same as that between germine and *iso*germine and between cevine and cevagenin.

Although the equilibrium position for the isomeric pair cevine and cevagenin must lie far on the side of cevine, Jaffé and Jacobs (*loc. cit.*) recently reported that cevine (α-cevine) was isomerised to " β-cevine " by alkali. We find that this so-called isomerisation is in fact the autoxidation of a few per cent. of the cevine to give a diosphenol chromophore (see Experimental). In agreement with this view Jaffé and Jacobs found that the infra-red spectra of cevine and " β-cevine " were identical, whilst the rotation of the latter was close to that for pure cevine. We conclude that " β-cevine " is simply slightly impure cevine.

The many oxygen functions in cevine naturally invite enquiry into the susceptibility of the alkamine and its derivatives to attack by glycol-splitting reagents. We have carried out a number of experiments with the results summarised in the Table.

The significance of the extensive consumption of lead tetra-acetate by cevine and dihydrocevine is not at once apparent. Some interesting conclusions were, however, reached from a study of the initial uptake of the reagent. It can be concluded from the

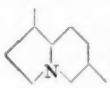
results for cevine, compared with those for dihydrocevine and for the betaine, that one of the two moles of lead tetra-acetate consumed so rapidly by cevine is involved in splitting the masked α-ketol grouping. Further, one of the acetate groups in cevine diacetate must be attached to the secondary hydroxyl group of the masked α-ketol system.*

	No. of moles of oxidant consumed		
	HIO_4	$Pb(OAc)_4$	
Compound	Final uptake after 24 hours	Initial uptake *	Final uptake †
Cevine	2·00	2·03	*ca.* 8·5
Dihydrocevine	—	1·09	*ca.* 8·5
Betaine	2·14	1·35	—
Cevine diacetate	1·06	1·00	2·88
Cevine tetra-acetate	—	0	0

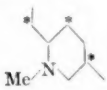
* Within 15 sec.; no further uptake in a period of minutes. † After 30 hours.

Seebeck and Stoll (*loc. cit.*) have recently shown that acetylation of cevine with perchloric acid as catalyst affords a tetra-acetate. We find that this compound is stable to chromic acid and so cannot contain a secondary hydroxyl group. Seebeck and Stoll also showed that cevagenin readily formed a triacetate. This must mean that that hydroxyl group of cevagenin which becomes the ether linkage of cevine is either primary or secondary in character [as already indicated in (I—VI)]. The stability of cevine tetra-acetate to chromic acid oxidation therefore implies, in addition, that both hydroxyl groups of the masked α-ketol system are acetylated. Thus the tetra-acetate contains nine oxygen atoms bound up in acetylated functions; the remaining three must be present as tertiary hydroxyl groups. Cevine diacetate is not stable to chromic acid. This we regard as due to the presence of the unacetylated tertiary hydroxyl group of the masked α-ketol system and/or to the presence of a not readily acetylated secondary hydroxyl group.

(VII)



(VIII)



(IX)

As to the relation of the oxygenated functions of cevine to the tertiary nitrogen atom, the following conclusion seems justified. Whilst soda–lime distillation of cevine afforded 2-ethyl-5-methylpiperidine (VII) (Jacobs and Craig, *J. Biol. Chem.*, 1938, **124**, 659) and a dicyclic base, $C_{10}H_{19}N$, possibly (VIII), similar degradation of the cevine betaine (*idem, ibid.*, 1938, **125**, 625) furnished only a *N*-methyl hydroxy-base, $C_9H_{19}ON$. The further degradation studies of Jacobs and Craig (*loc. cit.*) on this base indicate, when correctly interpreted, that the hydroxyl group is attached to a carbon atom β with respect to the nitrogen. Thus on Hofmann degradation of the corresponding methohydroxide a basic *oxide*, not an olefin, resulted. At least one of the positions marked with an asterisk in the formula (IX) for the base $C_9H_{19}ON$ must bear a hydroxyl group. Further studies on the constitution of cevine will be reported in due course.†

Experimental

M. p.s are uncorrected. Since the m. p.s of cevine and nearly all its derivatives depend on the rate of heating the standard technique of inserting the m. p. capillary tube 10° below the observed m. p. was adopted. Unless specified to the contrary, rotations were determined in acetone solution at room temperature, which varied from 15° to 25°. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Ultra-violet absorption spectra were measured in ethanol solution with a Unicam S.P. 500 Spectrophotometer. We are indebted to Dr. Keith Freeman of the University of California

* This secondary hydroxyl must be equatorial in character (see Barton, *Experientia*, 1950, **6**, 316) from the method of isolation of cevine (equilibration); it must, therefore, be easily acetylated. In principle the tertiary hydroxyl group of the masked α-ketol system might also be acetylated but, as a working hypothesis, we have tentatively assumed that the second acetate residue in the diacetate is attached elsewhere in the molecule.

† It is our understanding that this problem is also under investigation in the laboratories of the E.T.H., Zurich. We thank cordially Professor V. Prelog and Dr. O. Jeger for this information.

and Dr. A. R. H. Cole of the University of Western Australia for the determination of the infra-red spectra; the measurements were made on a Nujol mull unless specified to the contrary.

Electrometric titrations were carried out in 10% ethanol–water with the Cambridge pH meter.

For periodic acid titrations the procedure advocated by Jackson ("Organic Reactions," Vol. II, p. 361) was adopted. Freshly prepared aqueous solutions of periodic acid were used for each experiment, the alkamine derivative being dissolved in methanol. The composition of the reaction medium was adjusted to 50% aqueous methanol.

For long-term lead tetra-acetate reactions a standard solution, 0·058M with respect to lead tetra-acetate, in "AnalaR" acetic acid was used. The alkamine derivative was dissolved directly in the stock solution. The solutions were titrated according to the procedure of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1670).

For determination of the initial rate of uptake of lead tetra-acetate a somewhat different procedure was adopted. The alkamine derivative (approx. 0·03 mole) was dissolved in 1 : 1 (by vol.) aqueous acetic acid (1 ml.). To this solution was added with vigorous agitation, during 10 seconds, acetic acid (1 ml.) containing lead tetra-acetate (0·06 mole). After a further t seconds 3% potassium iodide in saturated aqueous sodium acetate (5 ml.) was added and the iodine liberated was titrated in the usual way. The appropriate blank determination, which, in fact, showed no consumption of lead tetra-acetate, was carried out in the same way. The time of reaction was regarded as $(t + 5)$ seconds. The experiments were also repeated with cevine and dihydrocevine in acetic acid alone without significant change in the uptake of lead tetra-acetate.

Isolation of Cevine.—Cevine was isolated from crude veratrine alkaloids (T. and H. Smith Ltd.) essentially according to Macbeth and Robinson's procedure (*J.*, 1922, **121**, 1571). To precipitate cevine from an aqueous solution of its potassium salt one must reduce the pH to only 9—10 by the addition of (solid) carbon dioxide. Further addition of carbon dioxide redissolves the cevine since it is a sufficiently strong base to be soluble in water at pH 8. Cevine was recrystallised slowly from dilute aqueous alcohol (yield : 35 g. from 100 g. of crude alkaloid esters). It had m. p. 172—176° decomp. (inserted at 160°), $[\alpha]_D$ −29° (*c*, 14·40), −29° (*c*, 5·00), −29° (*c*, 2·60). Macbeth and Robinson (*loc. cit.*) give $[\alpha]_D$ −30·8°. The equivalent weight (Found : 573) was determined by electrometric titration with 0·0501N-hydrochloric acid [Calc. for $C_{27}H_{43}O_8N,3{\cdot}5H_2O$ (see Freund and Schwarz, *Ber.*, 1899, **32**, 800): 571]. The pH at half-neutralisation was 9·74; pK_b 4·26. In the lead tetra-acetate oxidation experiments anhydrous and hydrated cevine gave the same rate of uptake of the reagent and the same final uptake.

Stability of Cevine to Bases.—Hydrated cevine (1·0 g.) in ethanol (5 ml.; previously saturated with sodium under reflux) was refluxed for 1 hour. Dilution of the solution with water and suitable extraction led to recovery of cevine (0·71 g., 79%), m. p. and mixed m. p. 170—175°, $[\alpha]_D$ −29° (*c*, 3·92).

Attempted Formation of Carbonyl Derivatives from Cevine.—Cevine was recovered unchanged [m. p. 170—178°, $[\alpha]_D$ −29° (*c*, 2·92)] after treatment with ethanolic semicarbazide acetate at room temperature for 5 days or after 2 hours' refluxing. Similar results were obtained with ethanolic 2 : 4-dinitrophenylhydrazine hydrochloride.

Preparation of Dihydrocevine.—Dihydrocevine, m. p. 260—265° (decomp.) (from concentrated methanolic solution), $[\alpha]_D$ −26° (*c*, 3·3 in MeOH), was prepared as described by Jacobs and Craig (*J. Biol. Chem.*, 1938, **125**, 625) except that ethanol was used instead of butanol. Dihydrocevine was conveniently purified through the *hydrochloride*. Recrystallised from ethanol–chloroform this had m. p. 255° (efferv.), $[\alpha]_D$ −18° (*c*, 1·8 in MeOH), −16° (*c*, 1·4 in MeOH) (Found : C, 59·05; H, 8·2; N, 2·7. $C_{27}H_{46}O_8NCl$ requires C, 59·15; H, 8·45; N, 2·6%). Dihydrocevine, crystallised from methanol, was titrated electrometrically with 0·0584N-hydrochloric acid (Found : equiv., 546. Calc. for $C_{27}H_{45}O_8N,CH_3{\cdot}OH$: equiv., 539). The pH at half-neutralisation was 9·65; pK_b 4·35. Dihydrocevine showed no selective absorption in the ultra-violet (even in the far ultra-violet) region, and showed no carbonyl band in the infra-red. Dihydrocevine does *not* reduce ammoniacal silver nitrate or Fehling's solution.

The Betaine from Cevine Methiodide.—Cevine methiodide, m. p. 250—253°, $[\alpha]_D$ −5° (*c*, 1·70 in MeOH), was prepared according to Jacobs and Craig's method (*loc. cit.*; cf. Freund and Schwarz, *J. pr. Chem.*, 1917, **96**, 236). It showed no carbonyl absorption in either the ultra-violet or the infra-red region. The derived betaine was prepared essentially according to Jacobs and Craig's method (*loc. cit.*) except that it was found necessary to heat the alkaline solution at 115° (internal temp.) in an oil-bath rather than on the steam-bath. The betaine,

after digestion with aqueous ethanol, had m. p. 265—268°, $\lambda_{max.}$ 280 mμ (ε, 70), and showed an intense carbonyl band at 1710 cm.$^{-1}$ in the infra-red.

The betaine was transformed into its hydrochloride, m. p. 245°, $[\alpha]_D$ −29° (*c*, 2·00 in MeOH), $\lambda_{max.}$ 280 mμ (ε, 58), as described by Jacobs and Craig (*loc. cit.*), and into its hydriodide by the following procedure. The betaine (300 mg.) in acetic acid (0·5 ml.) was admixed with aqueous potassium iodide (20%; 1 ml.). Crystallisation was induced by scratching. Next morning the highly crystalline *hydriodide* (280 mg.) had m. p. 250° (decomp.), $[\alpha]_D$ −27° (*c*, 1·91 in MeOH), $\lambda_{max.}$ 280 mμ (ε, 60) (Found: C, 51·25; H, 7·15; N, 2·2; I, 19·9. $C_{28}H_{46}O_8NI$ requires C, 51·6; H, 7·1; N, 2·2; I, 19·5%). The betaine hydriodide was mentioned by Freund and Schwarz (*J. pr. Chem.*, 1917, **96**, 236) who found m. p. 256° (decomp.) but gave no analytical data. On electrometric titration the betaine hydriodide behaved as a quaternary ammonium halide. Both the betaine hydrochloride and hydriodide showed intense carbonyl maxima in the infra-red region at 1710 cm.$^{-1}$.

Cevine Diacetate.—The diacetate, prepared as described by Freund (*Ber.*, 1904, **37**, 1946) and conveniently crystallised from ether, had m. p. 188—191°, $[\alpha]_D$ −4·5° (*c*, 15·5). It showed no ketonic or double-bond ultra-violet absorption (Found: C, 62·55; H, 8·4; N, 2·25; Ac, 14·85. Calc. for $C_{31}H_{47}O_{10}N$: C, 62·75; H, 8·0; N, 2·35; Ac, 14·5%).

Cevine diacetate (211 mg., 0·36 mmole) was treated with chromium trioxide (172 mg.) in water (10 ml.) and " AnalaR " acetic acid at 5°. With the aid of the appropriate blank the rate of consumption of chromic acid was shown to be as follows: 5 hr., 0·30 m.equiv.; 24 hr., 0·46 m.equiv.; 72 hr., 0·68 m.equiv. (theor. for 1 O: 0·72 m.equiv.).

Cevine Tetra-acetate.—Cevine tetra-acetate, m. p. 290—295°, $[\alpha]_D$ +38° (*c*, 3·56 in EtOH), and its perchlorate were prepared by Stoll and Seebeck's method (*loc. cit.*). The physical constants found by us are in good agreement with those recorded by them except that the perchlorate was found to have a double m. p. at 240° and 268°. Material melting at 240° is obtained when the salt is crystallised from water, but even this, if inserted below 240° and heated slowly, will fail to melt until about 260°. Material melting at 268° (decomp.) is obtained when the salt is crystallised from glacial acetic acid. A mixture of the two forms melts at the higher temperature without depression. The tetra-acetate shows no double-bond absorption in the far ultra-violet region. It was reconverted into cevine by alkaline hydrolysis.

Cevine tetra-acetate perchlorate (132 mg.) was treated with chromium trioxide (62 mg.) in water (3 ml.) and " AnalaR " acetic acid (5 ml.) at 5°. During 24 hours the consumption of chromic acid was <10% of that required for one atom of oxygen. Cevine tetra-acetate was recovered (70%) unchanged from the solution and characterised as the perchlorate, m. p. 240°.

Autoxidation of Cevine in Alkaline Solution.—A solution of " AnalaR " sodium hydroxide (1·5 g.) in water (15 ml.; oxygen-free) and ethanol (100 ml.; oxygen-free) was prepared. Cevine (200 mg.) was dissolved in this solution (20 ml.). In two parallel experiments one batch of cevine solution was kept under nitrogen in a stoppered flask, the other briefly aerated with carbon dioxide-free air and then stored under carbon-dioxide-free air (cf. Jaffé and Jacobs, *loc. cit.*). After 12 days the two solutions, after dilution with the appropriate amount of 0·05N-sodium hydroxide in 95% ethanol, had $\lambda_{max.}$ 300—305 mμ (ε, 70 and 710 respectively). The latter intensity is far too great to be due to an isolated carbonyl group and the position of the maximum is also somewhat displaced. When the solutions were acidified with concentrated hydrochloric acid the position of the maxima at once changed to 275—280 mμ and the intensity of absorption increased by 15% in both cases. The shift, and, in particular, the change in relative intensity are characteristic of the diosphenol chromophore rather than of the phenol chromophore (Eastham, to be published) where the relative intensity shift is inverted. Diosphenols have $\lambda_{max.}$ 10,000 ± 3000 so that only a few per cent. of diosphenol are produced in the autoxidation. In several repetitions of these experiments on a larger scale cevine was recovered unchanged in good yield. In a typical experiment it had m. p. 163—168°, $[\alpha]_D$ −30° (*c*, 1·64), and showed no selective ultra-violet absorption.

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, September 16th*, 1952.]

87. *The Mechanism of the Bromination of Ethyl Malonate.*

By R. P. Bell and M. Spiro.

The kinetics of the base-catalysed bromination of ethyl malonate have been studied in aqueous solutions at 25° over the pH range 1·7—4·5 and with bromine concentrations of 10^{-4}—10^{-3}M. In this range the velocity varies with bromine concentration, and is thus no longer determined solely by the rate of ionization or enolization of the ester. The variation of rate with bromine concentration and with pH can be accounted for quantitatively by supposing that both the anion and the enol react with bromine. The main brominating species is molecular bromine, but there is a small contribution from the less active species Br_3^- and HOBr. At pH >3 most of the bromination takes place through the anion, while at pH <3 the enol is more important. Absolute rate constants are estimated for the bromination reactions. Bartlett and Vincent's results for the chlorination of ketones in alkaline hypochlorite have been re-interpreted, and estimates made of the velocity constants involved.

The halogenation of compounds containing a reactive $\geqslant$CH group, *e.g.*, ketones and keto-esters, is usually kinetically of zero order with respect to halogen. The rate-determining step must therefore be the formation of a reactive intermediate, but there is still some doubt whether this intermediate is the enol or the anion of the original substance. Lapworth (*J.*, 1904, **85**, 30) supposed that halogenation involved the formation of enol, and this view has been widely accepted. The usual modern interpretation (see, *e.g.*, Bell, "Acid-Base Catalysis," Oxford, 1941, p. 135) distinguishes between catalysis by acids and by bases. In acid catalysis the formation of enol is believed to be rate-determining, but in basic catalysis the anion is thought to be the species which is halogenated, since it is an intermediate in the formation of the enol and would be expected to halogenate even more rapidly. Thus Hammett ("Physical Organic Chemistry," New York, 1940, p. 231) writes: "There is no reason to suppose that the formation of an electrically neutral enol form represents anything more than an unimportant by-path into which a portion of the reacting substance may transiently stray." However, this view does not depend on direct kinetic evidence, and cannot be tested as long as the reaction remains of zero order with respect to halogen; it is also impossible to obtain evidence by studying directly the halogenation of pure enols or anions of ketonic substances, since these reactions are much too fast to follow by ordinary methods.

A test is possible in principle if a reaction can be found in which the enolization or ionization is not wholly rate-determining. West (*J.*, 1924, **125**, 1277) showed that in the bromination of malonic acid the rate of introduction of the first bromine atom is independent of bromine concentration, but that the subsequent bromination of monobromomalonic acid is of first-order with respect to bromine. He concludes that the reactive species concerned are the enols, but the interpretation is complicated by the two stages of dissociation of the acids concerned. Further information comes from the work of Bartlett (*J. Amer. Chem. Soc.*, 1934, **56**, 967) and of Bartlett and Vincent (*ibid.*, 1935, **57**, 1596) on the halogenation of acetone and other ketones in alkaline hypochlorite solutions. In these solutions the rate of ionization and enolization is increased by the high value of $[OH^-]$, and the halogenating power of the solution is decreased by the conversion of Cl_2 into HOCl and OCl^-: correspondingly it was found that in the neighbourhood of pH 10 the reaction became of first order with respect to halogen. The variation of rate with pH should give information about the nature of the reacting species, but does not provide an unambiguous answer, since the two reactions enol + OCl^- and anion + HOCl are kinetically indistinguishable. Bartlett's results are reconsidered on p. 434.

It would be of interest to discover which species react with the more usual halogenating species Br_2 and I_2, and this is possible in principle if measurements can be made at sufficiently low halogen concentrations. With most ketonic substances the reaction velocity remains independent of halogen concentration down to very low values of the latter, but it

has been observed (Bell, Everett, and Longuet-Higgins, *Proc. Roy. Soc.*, 1946, *A*, **186**, 443) that in the bromination of ethyl malonate the velocity falls off noticeably with bromine concentrations less than about 0·01M. Preliminary work in this laboratory by Mr. D. R. Mayne showed that the reaction in dilute bromine solutions could be interpreted in terms of two consecutive steps, and the present paper reports a quantitative study of the effect of bromine concentration and pH.

It is convenient to consider first the kinetic behaviour expected. Suppose that the substance RH can be brominated to RBr through either the anion R^- or the enol HR, and that the only reactive bromine species is Br_2. (It will be shown later that in the bromination of malonic ester the observed rate is determined mainly by the substitution of the first bromine atom, though a small correction is necessary to allow for the fact that the rate of bromination of the monobromo-ester is not infinitely great: similarly, a small correction is necessary for bromination by the species Br_3^- and HOBr.) If the solution contains a number of acid–base pairs A_i–B_i, the kinetic scheme for basic catalysis is

$$\left.\begin{aligned} &RH + \Sigma B_i \underset{k^i_{-1}}{\overset{k^i_1}{\rightleftharpoons}} R^- + \Sigma A_i \underset{k^i_{-2}}{\overset{k^i_2}{\rightleftharpoons}} HR + \Sigma B_i \\ &R^- + Br_2 \xrightarrow{k_3} RBr + Br^- \\ &HR + Br_2 \xrightarrow{k_4} RBr + Br^- + H^+ \end{aligned}\right\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where the k's are all second-order velocity constants. We shall assume initially that the second step in the above scheme is effectively in equilibrium, *i.e.*, that the dissociation equilibrium between the enol HR and the ion R^- is set up very rapidly and is not disturbed by the removal of HR or R^- by bromination. This is reasonable, since the ionization of the enol involves no electronic rearrangement (cf. Bell and Higginson, *Proc. Roy. Soc.*, 1949, *A*, **197**, 141). Making this assumption, we have throughout the reaction $[R^-]/[HR] = K_{HR}/[H^+]$, where K_{HR} is the acid dissociation constant of the enol. Applying the steady state conditions $d[R^-]/dt = d[HR]/dt = 0$ (since for malonic ester $[R^-]$ and [HR] are throughout vanishingly small) we find for the observed velocity constant v

$$\begin{aligned} v = \frac{1}{[RH]}\frac{d[RBr]}{dt} &= \{k_3[R^-][Br_2] + k_4[HR][Br_2]\}/[RH] \\ &= \frac{[Br_2]\Sigma k^i_1[B_i]\{k_3 + k_4[H^+]/k_{HR}\}}{[Br_2]\{k_3 + k_4[H^+]/K_{HR}\} + \Sigma k^i_{-1}[A_i]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2) \end{aligned}$$

At high bromine concentrations the observed velocity becomes $v_\infty = \Sigma k^i_1[B_i]$. We have for each acid–base pair $k^i_{-1}/k^i_1 = [B_i][H^+]/[A_i]K_{RH}$, where K_{RH} is the dissociation constant of the substance RH, and we can also write $K_{RH}/K_{HR} = K_E$, where K_E is the equilibrium enol : keto ratio. If we define a quantity $F = [Br_2](v_\infty - v)/vv_\infty$, equation (2) becomes

$$1/F = vv_\infty/[Br_2](v_\infty - v) = k_4K_E + k_3K_{RH}/[H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The above reaction scheme can therefore be tested by investigating the dependence of the experimental quantity F on $[H^+]$.

If we do not make the simplifying assumption that the second step in (1) is at equilibrium, we obtain instead of (3) the equation

$$\frac{1}{F} = \frac{k_4K_E}{1 + k_4[Br_2]/\Sigma k^i_{-2}[B_i]} + \frac{k_3K_{RH}}{[H^+]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

so that in this case the observed value of F will depend not only on $[H^+]$, but also on the concentration of bromine and of the bases present. It should thus be easy to test whether the assumption involved in (3) is justified.

Experimental

Ethyl malonate was redistilled (b. p. 104·5°/30 mm.) Ethyl monobromomalonate, prepared as described in *Org. Synth.*, Coll. Vol. I, 1st edn., p. 240, was redistilled (b. p. 109—110°/7·5 mm.). Acetic acid, monochloroacetic acid, and the inorganic reagents used were of "AnalaR"

quality, and all solutions were made up with conductivity water. Enough potassium nitrate was added to each reaction mixture to bring the total ionic strength up to 0·1. Stock solutions of the esters were not kept for more than a few days, in order to avoid hydrolysis. Solutions of acids and of sodium hydroxide were standardized, constant-boiling hydrochloric acid being used as the primary standard. Sodium thiosulphate solution was periodically standardized against potassium iodate.

In order to avoid loss of bromine by evaporation, the kinetic measurements were carried out in a 20-ml. all-glass Pyrex syringe, with a suitably bent capillary fused to the nozzle. The arrangement of the syringe in the thermostat (25° ± 0·02°) is indicated in Fig. 1. Only a minute air bubble remained in the syringe after filling, and tests showed that no detectable amount of bromine was lost during an experiment. Samples for analysis were expelled into a weighed flask containing 1 ml. of a 1M-acetate buffer (1 : 1) and at least a three-fold excess of allyl alcohol to remove free bromine. A few crystals of potassium iodide were added from a weighed dish, and after the flask had been re-weighed the iodine liberated by the bromo-esters was titrated at 30-min. intervals with N/500-thiosulphate, as described by Bell, Everett, and Longuet-Higgins (*loc. cit.*). The same results were obtained by using Bell, Smith, and Woodward's iodate titration method (*Proc. Roy. Soc.*, 1948, *A*, **192**, 479).

In each experiment at least one sample was analysed without the addition of allyl alcohol in order to determine the total oxidizing power, which should be equivalent to the amount of bromine initially present. Identical results were obtained with samples taken near the beginning and near the end of an experiment, showing that no bromine had been lost by evaporation.

We shall describe first the experiments with relatively high concentrations of bromine (~0·02M) which give the value of v_∞ in equation (3). When monobromomalonic ester is the starting material there are no complications arising from successive stages of bromination, and the reactions should therefore be of first order with respect to the ester. This was found to be so for the earlier part of the reaction, though the rate fell off towards the end of each reaction. However, only very dilute solutions of ester could be used (~4×10^{-4}M), so the accuracy is not high. The chief purpose of the experiments with monobromomalonic ester was to obtain a correction to apply to the results for malonic ester, and the accuracy is ample for this purpose. The results obtained are given in Table 1. In this, and in all subsequent tables, the symbols have the following meanings: r = stoicheiometric buffer ratio, [acid]/[anion]; [B⁻] = mean concentration of anion, corrected for the acid produced during the reaction; v = first-order velocity constant, min.$^{-1}$; v_0 = velocity constant of water-catalysed reaction; k_{B^-} = catalytic constant of anion.

TABLE 1. *Bromination of monobromomalonic ester at high bromine concentrations.*

[Ester] ~4×10^{-4}M, [bromine] ~0·02M.

In 0·0011N-$HClO_4$, 10^4v = 161, 161, 145; mean 10^4v = 156.

	r	10^4[B⁻]	10^4v	k_{B^-}	Mean		r	10^4[B⁻]	10^4v	k_{B^-}	Mean
Monochloro-acetate buffers	1·02	519	366	0·405	0·415	Acetate buffers	1·12	19·5	364	10·7	10·1
	1·02	519	373	0·418			1·07	38·6	532	9·5	
	1·74	536	382	0·422							

The value obtained for v_0 agrees much better with that given by Bell, Gelles, and Möller (*Proc. Roy. Soc.*, 1949, *A*, **198**, 308; $v_0 = 181 \times 10^{-4}$ in our units) than with that of Pearson and Mills (*J. Amer. Chem. Soc.*, 1950, **72**, 1692), *viz.*, $v_0 = 86 \times 10^{-4}$. The latter workers prepared the monobromo-ester *in situ* by adding less than one equivalent of bromine and allowing the solution to stand " until equilibrium was reached," after which the rate of further bromination was measured. However, it is likely that equilibrium was not attained, since the first addition of bromine will initially form dibromo-ester, which then reverts slowly to monobromo-ester. If the solution contained less monobromo-ester than was believed the observed rate would be too low.

In the bromination of malonic ester the rate is mainly determined by the first stage of the reaction, but a small correction is necessary for the finite rate of bromination of the monobromo-ester. The method of estimation used gives the total oxidizing power of the monobromo- and dibromo-ester. If this is x equiv./l. and the initial ester concentration is c, the course of the reaction is given by

$$2(R-1)(c-\tfrac{1}{4}x)/c = (2R-1)\,e^{-vt} - e^{-v't} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

(cf. Pedersen, *J. Phys. Chem.*, 1933, **37**, 751; Bell, Gelles, and Möller, *loc. cit.*), where v and v'

are the first-order constants for the two stages of bromination (at high bromine concentrations), and $R = v'/v$. Equation (5) can be re-written in the form

$$vt = Q + \Delta Q, \quad Q = \ln (1 - \tfrac{1}{2}x/c)$$
$$\Delta Q = \ln \{1 + (1 - e^{-(R-1)vt})/2(R - 1)\} \quad . \quad . \quad . \quad . \quad . \quad (6)$$

ΔQ is a correction term to allow for the fact that v' is not infinite. As t increases, ΔQ approaches the constant value $\ln \{1 + 1/2(R - 1)\}$, and a plot of Q against t thus approaches a slope v.

The values of v in Table 2 were obtained by plotting $Q + \Delta Q$ against t; ΔQ was calculated by successive approximations, using first an approximate value of v and a value of v' from Table 1. These plots were linear, but had a small negative intercept (0·002—0·005) at $t = 0$ (cf. Fig. 2). This was due to the fact that at the end-point of the titration a small amount of iodine remained combined with the malonic ester and the allyl alcohol. The magnitude of the intercept agrees with that calculated from the known equilibrium constants for these iodinations (Bell and Gelles, *Proc. Roy. Soc.*, **1951**, *A*, **210**, **310**; Berthoud and Mosset, *J. Chim. physique*, 1936, **33**, **272**), and does not affect the slope of the plot since it remains approximately constant throughout the reaction.

FIG. 1.

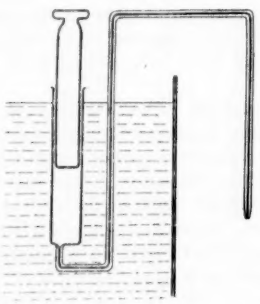
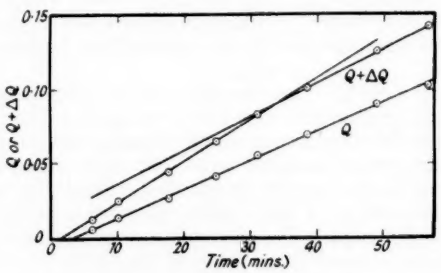


FIG. 2.



The data in Table 2 show good agreement with the earlier results of Bell, Everett, and Longuet-Higgins (*loc. cit.*), who followed the reaction up to about two-thirds completion, and neglected the correction ΔQ, whereas the present work deals chiefly with the first few units % of the reaction, where this correction is important. The agreement between the two sets of results justifies the method of applying the correction.

TABLE 2. *Bromination of malonic ester at high bromine concentrations.*

[Bromine] ~ 0·02M. Values of v in parentheses are calculated from the catalytic constants given by Bell, Everett, and Longuet-Higgins (*loc. cit.*).
In 0·02M-$HClO_4$: 10^4 [ester] = 29·7, 44·0, 63·8; $10^4 v$ = 13·9, 14·3, 14·5; mean 14·2 (14·3).

	10^4[ester]	r	10^4[B^-]	$10^4 v$	Mean	
Monochloroacetate buffers...	10·0	1·03	515	35·2		
	49·0	1·03	515	36·2	36·1	(36·8)
	50·0	1·03	515	36·9		
	50·0	1·03	219	23·7	23·7	(23·9)
Acetate buffers	3·46	6·18	200	290	290	(285)
	3·94	6·18	200	291		

The remaining experiments are concerned with the bromination of the malonic ester at low bromine concentrations where v and v_∞ differ appreciably. The experimental method is the same as before, and the values of v have again been obtained by plotting $Q + \Delta Q$ against t, the data in Tables 1 and 2 being used for calculating R. This procedure is not strictly justified, since we are no longer dealing with consecutive first-order reactions. However, the correction ΔQ is not large, except in the very early stages of the reaction, and some rough experiments showed that the ratio v/v_∞ has similar values for malonic ester and monobromomalonic ester under the same conditions. The values of v should therefore not be subject to any appreciable error.

Fig. 2 shows typical plots of Q and of $Q + \Delta Q$ against time. The former is fortuitously linear, but the slope of the latter decreases with time because of the decreasing bromine concentration. It is possible to integrate equation (2) to represent the course of the reaction, but

the expression obtained is cumbrous, and we have preferred to obtain v for different bromine concentrations by measuring the slope of the plot over a range of points. In this way two (and sometimes three) values of v were obtained from each experiment. Examples of the results obtained are given in Table 3. In the buffer solutions the values of $[H^+]$ are calculated from the thermodynamic dissociation constants $K(CH_3{\cdot}CO_2H) = 1{\cdot}751 \times 10^{-5}$, $K(CH_2Cl{\cdot}CO_2H) = 1{\cdot}385 \times 10^{-3}$, $f_\pm$ being taken as 0·76; v_∞ is obtained from Table 2 by a small extrapolation (<2%) to infinite bromine concentration. In calculating v for the most strongly acid solutions we have applied a small correction (~2%) for the acid hydrolysis of the malonic ester. This followed the treatment of Bell, Everett, and Longuet-Higgins (*loc. cit.*) except that the rate of hydrolysis of the dibromo-ester was assumed to be much smaller than that of the unsubstituted ester.

The values of F in the table are calculated from $F = [Br_2](v_\infty - v)/vv_\infty$. In each series a few experiments were done with much higher concentrations of bromide ion. This produces a slight decrease of velocity because of the conversion of Br_2 into the less reactive Br_3^-. In addition, in the series with acetate buffers a few experiments were done with very low values of $[Br^-]$, thus favouring the formation of HOBr, which was also found to be less reactive than Br_2. These experiments do not provide any accurate measurement of the reactivity of Br_3^- or HOBr, but they are sufficient to correct for the small amounts of these species present in the remaining experiments. (No evidence was found for bromination by any other species, such as H_2OBr^+ or $CH_3{\cdot}CO_2Br$.) The column headed F(corr.) in Table 3 represents the values which would have been obtained if all the bromine had remained in the form of Br_2: it will be seen that they differ little from the values directly observed.

TABLE 3. (*Typical results.*) *Bromination of malonic ester at low bromine concentrations.*

c = initial ester concentration; other concentrations are mean values.

10^4c	$10^4[Br_2]$	$10^4[Br^-]$	10^4v	10^3F	10^3F (corr.)	10^4c	$10^4[Br_2]$	$10^4[Br^-]$	10^4v	10^3F	10^3F (corr.)
Series 2: 0·0081M-$HClO_4$; $10^4v_\infty = 14{\cdot}3$.											
71·8	6·39	27·6	12·8	52	51		1·49	33·8	9·0	61	60
	3·22	30·8	11·1	65	64	36·2	1·86	8·6	10·3	50	50
51·2 *	3·81	30·9	12·1	48	47		0·81	9·7	7·4	53	53
	1·63	33·1	9·7	54	53	52·0	3·93	731	11·7	61	—
50·5	3·72	31·1	12·0	50	49		1·88	733	9·1	75	—
									Mean	53 ± 2	
Series 7: Acetate buffer; $r = 6{\cdot}18$, $10^4[B^-] = 200$, $[H^+] = 1{\cdot}87 \times 10^{-4}$, $10^4v_\infty = 296$.											
5·51	6·65	51·3	193	12·0	11·4	4·97	2·00	18·6	113	10·9	10·6
	4·58	53·4	162	12·8	12·1		1·04	19·6	73	10·7	10·4
3·75	4·01	30·7	164	10·9	10·5	5·02	4·05	731	140	15·2	—
	2·90	31·8	130	12·5	12·1		2·78	732	104	17·3	—
									Mean	11·2 ± 0·3	

* In these experiments HCl was used in place of $HClO_4$.

DISCUSSION

The data for monobromomalonic ester at high bromine concentrations (Table 1) can be compared with similar data for other substrates (cf. table given by Bell, Gelles, and Möller, *loc. cit.*, p. 321). The velocity of the anion-catalysed reaction is intermediate between those for ethyl malonate and ethyl acetoacetate, and the same is true for the exponent α, since the catalytic constants for the two anions can be represented by $k_{B^-} = 3{\cdot}40 \times 10^{-3}\,(1/K_{HB})^{0{\cdot}73}$.

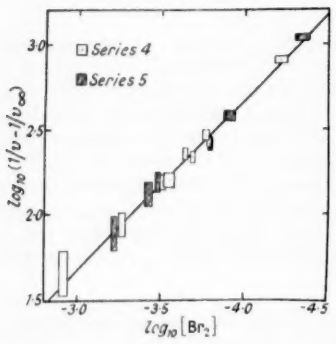
With regard to the data for low bromine concentrations, the first-order constants in Table 3 show the expected falling off, and are almost proportional to the bromine concentration at very low values of the latter. In Series 4 the ester concentration was varied by a factor of 15 without producing any change in the value of F. Fig. 3 shows a plot of $\log(1/v - 1/v_\infty)$ against $\log[Br_2]$ for series 4 and 5. The size of the rectangles represents an error of ±3% in v and ±1% in $[Br_2]$. The agreement with a straight line of slope unity confirms that the kinetics involve two consecutive reactions [cf. equation (3)]. The same point is illustrated by the constancy of F within any one series. The individual variations in F appear rather large, but it must be remembered that errors in the velocity are magnified several times in F, especially when v is close to v_∞. The errors attached to the mean F values in Table 3 are standard deviations calculated by the usual methods.

Table 4 contains a summary of the mean F values. The variation of F with $[H^+]$ is of the type expressed by equation (3), and the values of F (calc.) in Table 4 are those given by

$$1/F = 15{\cdot}5 + 0{\cdot}0136/[H^+] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where the best values of the constants have been obtained by applying the method of least squares to the weighted values of F (obs.) (cf. Birge, *Phys. Review*, 1932, **40**, 207). The comparison of series 4 and 5 in Table 4 and Fig. 3 shows that F is independent of the catalyst concentration: since we have already seen that it is independent of $[Br_2]$, the simplifying assumption made in deriving equation (3) is justified, and it is not necessary to use the more complicated equation (4).

FIG. 3.



The presence of two terms in equation (7) shows that both the enol and the anion are involved as reactive intermediates in the base-catalysed bromination, their relative importance varying with pH. At pH >3 most of the bromination takes place through the anion, while at pH <3 the enol is more important. This conclusion will still be valid at high bromine concentrations, provided that the assumption underlying equation (3) still holds. By comparing equations (3) and (7) we can obtain some information about the absolute rates of bromination of the anion and the enol (k_3 and k_4). Pearson and Mills (*loc. cit.*) give $K_{RH} \sim 5 \times 10^{-14}$ for malonic ester, whence $k_3 \sim 3 \times 10^{11}$ l. mole^{-1} min.$^{-1}$. This represents an extremely fast reaction, being only some 50 times smaller than the gas collision number expressed in these units. There are no direct estimates of K_E for malonic ester, but we can estimate it tentatively at 10^{-6}—10^{-4} if we assume that the enol form has a dissociation constant in the range 10^{-10}—10^{-8} (cf. Schwarzenbach and Felder, *Helv. Chim. Acta*, 1944, **27**, 1044). This gives $k_4 \sim 10^5$—10^7 l. mole^{-1} min.$^{-1}$, *i.e.*, the reaction of bromine

TABLE 4. *Summary of data for bromination of malonic ester.*

Series	r	$10^4[B^-]$	$[H^+]$	10^4v_∞	No. of expts.	Mean of 10^3F (obs.)	10^3F (calc.)
Perchloric acid.							
1	—	—	$2{\cdot}00 \times 10^{-2}$	14·3	20	58 ± 3	62
2	—	—	$8{\cdot}10 \times 10^{-3}$	14·3	10	53 ± 2	58
Monochloroacetate buffers.							
3	3·56	278	$8{\cdot}10 \times 10^{-3}$	26·2	11	67 ± 3	58
4	1·03	515	$2{\cdot}46 \times 10^{-3}$	36·4	12	48 ± 1	48
5	1·03	219	$2{\cdot}46 \times 10^{-3}$	23·7	11	48 ± 1	48
6	0·352	503	$8{\cdot}43 \times 10^{-4}$	35·9	10	28 ± 1	32
Acetate buffers.							
7	6·18	200	$1{\cdot}87 \times 10^{-4}$	296	8	11·2 ± 0·3	11·3
8	3·13	199	$9{\cdot}48 \times 10^{-5}$	296	10	7·0 ± 0·5	6·3
9	1·07	198	$3{\cdot}24 \times 10^{-5}$	295	11	2·4 ± 0·2	2·3

with the enol is much less efficient than with the anion, as might be expected. The data in Table 3 suggest that Br_3^- reacts about two-thirds as fast as Br_2 with the enol, and even less rapidly with the anion, while HOBr appears to react roughly half as fast as Br_2 with the anion. These conclusions are reasonable, but are subject to some uncertainty because of the small experimental differences involved.

Bartlett and Vincent's data (*loc. cit.*) for the chlorination of ketones in alkaline hypochlorite solutions can be expressed in the form $k = a/[OH^-] + b + c[OH^-]$, where k is the observed second-order velocity constant. The authors attribute the second and third terms to the reactions enol + OCl^- and anion + OCl^- respectively, but do not give any interpretation of the term $a/[OH^-]$. This must be due to the reaction enol + HOCl, and if we accept Schwarzenbach and Wittwer's estimate (*Helv. Chim. Acta*, 1947, **30**, 669) for

the enol content of acetone, we obtain $k \sim 10^{11}$ l. mole^{-1} min.$^{-1}$ for this reaction. Similarly, taking pK = 19 for acetophenone and pK = 20 for acetone (McEwen, *J. Amer. Chem. Soc.*, 1936, **58**, 1124; Bell, *Trans. Faraday Soc.*, 1943, **39**, 253), we find $k \sim 10^{7}$ l. mole^{-1} min.$^{-1}$ for the reaction of hypochlorite ion with the anion of either of these ketones. The interpretation of the second term b is ambiguous, since the reaction enol + OCl$^-$ suggested by Bartlett and Vincent is kinetically indistinguishable from anion + HOCl. For acetone the velocity constants can be estimated as 10^6 and 10^{12} l. mole^{-1} min.$^{-1}$ respectively, so that either would be kinetically possible.

We thank the Royal Commission for the Exhibition of 1851 for the award of an Overseas Scholarship to one of us (M. S.).

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88. *Stages in Oxidations of Organic Compounds by Potassium Permanganate. Part I. The Permanganate–Manganate Stage. Part II. The Manganic–Manganous Stage.*

By ALAN Y. DRUMMOND and WILLIAM A. WATERS.

This investigation has as its object the elucidation of the particular characteristics of the stages involved in the reduction $MnO_4^- + 8H^+ + 5e \longrightarrow Mn^{2+} + 4H_2O$ by discovering the responses of different organic groups to isolated valency changes of manganese.

Part I. The $MnO_4^- \longrightarrow MnO_4^{2-}$ stage in alkaline permanganate oxidation of organic compounds has been studied by using Ba^{2+} to arrest further degradation of MnO_4^{2-}, and an improved titrimetric method depending on the rapid oxidation $2MnO_4^- + CN^- + H_2O = 2MnO_4^{2-} + CNO^- + 2H^+$ has been worked out.

All classes of organic compound except ethers, saturated carboxylic acids, including oxalic and pyruvic acid, and tertiary monohydric alcohols are oxidised considerably. Aldehydes and ketones undergo stepwise degradation, probably by attack on enolic structures. Olefinic compounds do not reduce MnO_4^- beyond the MnO_4^{2-} stage, as would be expected for a mechanism involving addition of MnO_4^- to the double bond (cf. OsO_4).

Part II. The oxidising action of manganic sulphate has been studied qualitatively; acid manganic pyrophosphate solution is a suitable reagent for the kinetic study of organic oxidation processes. Manganic salts do not oxidise olefins, formic acid, or alcohols other than 1 : 2-glycols. The reaction between manganic pyrophosphate and aldehydes is of zero order with respect to Mn^{3+} but of first order with respect to both RCHO and H^+. Oxidation continues beyond the stage $RCHO \longrightarrow RCO_2H$, and a mechanism involving enolisation is proposed.

OXIDATIONS of organic compounds by potassium permanganate are usually multi-stage processes, for the degradation of organic molecules proceeds by the rupture of discrete two-electron bonds whilst the manganese undergoes an overall 5-electron transition, $MnO_4^- \longrightarrow Mn^{2+}$, in acid solution, or a three-electron transition, $MnO_4^- \longrightarrow MnO_2$, in neutral or alkaline solution. Other manganese ions of intermediate valency must undoubtedly intervene, though very little is known about them. The manganic cation, Mn^{3+}, is certainly involved in many of the rate-determining processes in acid solution, and Guyard's reaction, $2MnO_4^- + 3Mn^{2+} + 4OH^- = 5MnO_2 + 2H_2O$, becomes important in neutral and alkaline solutions. Moreover, Polissar's work (*J. Amer. Chem. Soc.*, 1936, **58**, 1372) with radioactive manganese has made it clear that some of the reactions involved in permanganate reduction by manganese salts are not reversible, for although there is a rapid radioactive exchange between Mn^{2+}, Mn^{3+}, and Mn^{4+} ions in solution, yet there is no exchange between MnO_4^- and Mn^{3+} or Mn^{2+}.

Now since the anions, MnO_4^- and MnO_4^{2-}, of the high-valency states of manganese and the cations, Mn^{4+} and Mn^{3+}, of the lower-valency states are structurally so different, it is

rational to suppose that their chemical reactivities should also differ in type. Consequently, amongst oxidations of organic compounds it should be possible to discover features characteristic of identifiable valency changes. Some diagnostic evidence is available already. Launer and Yost (*J. Amer. Chem. Soc.*, 1934, **56**, 2571) showed that the induction period preceding the oxidation of oxalic acid by acid permanganate can be prolonged almost indefinitely by adding fluoride anions to form complexes with manganese cations, thus proving that MnO_4^- anions do not oxidise oxalic acid. Again, Merz, Stafford, and Waters (*J.*, 1951, 638) have shown that the acid permanganate oxidation of alcohols can be promoted by ferrous ions or hydrogen peroxide, and probably requires the presence of Mn^{4+}. Further evidence concerning the individual stages in oxidations by either acid or alkaline permanganate can be obtained by the study of reactions involving limited valency changes. In strongly alkaline solution it is possible to study the one-electron change $MnO_4^- \longrightarrow MnO_4^{2-}$ by Stamm's method (*Z. angew. Chem.*, 1934, **47**, 579, 791; see "Newer Methods of Volumetric Analysis," trans. by Oesper, Van Nostrand Co. Inc., New York, 1938) using the insolubility of barium manganate to minimise further oxidations by MnO_4^{2-}. Again, in concentrated (>9N) sulphuric acid the cherry-red manganic cation, Mn^{3+}, is stable enough for titrimetric use (Ubbelohde, *J.*, 1935, 1605) but is not so convenient as the complex manganic pyrophosphates which can be used in aqueous solutions at acidities down to pH 6 (Kolthoff and Watters, *Ind. Eng. Chem. Anal.*, 1943, **15**, 8; *J. Amer. Chem. Soc.*, 1948, **70**, 2455) but yet are so loosely complexed (Taube, *Chem. Reviews*, 1952, **50**, 69) that they still exhibit, though with much less vigour, the oxidising actions of manganic cations. Table 1 shows that in this way it is possible to pick out certain distinctive properties of MnO_4^- and Mn^{3+} ions; *e.g.*, MnO_4^- does not attack oxalates but Mn^{3+} does so, whereas the converse holds for the attacks of these two ions upon olefinic links. Other features of these oxidations are discussed in detail below.

TABLE 1. *Oxidations of organic compounds with potassium permanganate and manganic compounds.*

Compound	$KMnO_4$, alkaline	$Mn_2(SO_4)_3$ in conc. H_2SO_4	$Mn(H_2P_2O_7)_3^{3-}$ in 0·2-NH_2SO_4	Acid $KMnO_4$		
				N-H_2SO_4	+ F^-	+ $H_4P_2O_7$
Diethyl ether	O	O	O	I, S, B	ss, R	ss, R
Dioxan	O	F	S	I, S, B	sss, R	sss, R
Methanol	+	O	O	I, S, T→B	ss, B	ss, R
Ethanol	+	O	O	I, S, T→B	ss, B	ss, R
tert.-Butanol	O	O	O	I, S, T→B	ss, B	ss, R
Ethylene glycol	+	+	O	I	S	ss, R
1 : 2-Butylene glycol	+	F	S	I	ss	ss, R
Pinacol	+	+	+	+	ss	ss
Propaldehyde	+	+	+	F	F, R	F, R
n-Butaldehyde	+	+	+	F	F, R	F, R
Formaldehyde	+	ss	O	F	F, R	F, R
Formic acid	+, F	O	O	S	ss	ss
RCO_3H	O	O	O	(O)	O	O
Acetone	+	S	S	I, ss→B	sss, R	sss, R
Ethyl methyl ketone	+	S	+(B)	I, S, B	ss, R	sss, R
Pyruvic acid	O	F	O	I, F	I ?S	I, ?S
Glycollic acid	+	S	S	I, T→B	S	S
Malonic acid	+	+	+	I, +	I, S	I, S
Oxalic acid	O	+	F	I, F	I ?S	I, ?S
Maleic acid	+	O	O	F +	F, T	F, T
Fumaric acid	+	O	O	F +	F, T	F, T
Cinnamic acid	+	O	O	F, B	F, T	F, T
Phenol	+	VF, B	VF, B	F +	F, +	F, +
$MeNH_2$,HCl	+	B, ss	O	ss, B	ss	ss
Me_2NH,HCl	+	B, ss	O	ss, B	ss	ss

Key to reactions of Table 1.

+, Definite reaction. O, No oxidation. F, Fast reaction. S, Slow reaction.
I, Induction period before reaction. ss, Very slow. sss, Just perceptible.
T, Transient red colour (? manganic ion). R, Residual red colour (? manganic ion).
B, Brown precipitate or colour (? MnO_2).

Note. All the reactions with manganic pyrophosphate were measurably slow, and were usually tested at 40—50°. The other reactions were examined at room temperature.

Part I. Oxidation by Alkaline Permanganate

Holluta (*Z. physikal. Chem.*, 1922, **101**, 34; **102**, 276; Holluta and Weiser, *ibid.*, **101**, 489) showed that in weak acid or alkali the initial stage in the reaction between potassium permanganate and formic acid was kinetically of first order in respect to both MnO_4^- and $H{\cdot}CO_2^-$ ions. It gave green MnO_4^{2-} which then reacted more slowly to give hydrated manganese dioxide with slight evolution of oxygen under alkaline conditions. Stamm (*loc. cit.*) then showed that, in concentrated alkali, oxidation by MnO_4^{2-} was so slow that barium nitrate or chloride was able to remove MnO_4^{2-} quantitatively as barium manganate, and he used alkaline permanganate for effecting quantitative oxidations such as: $IO_3^- \longrightarrow IO_4^-$, $I^- \longrightarrow IO_4^-$, $PO_3^{3-} \longrightarrow PO_4^{3-}$, $AsO_3^{3-} \longrightarrow AsO_4^{3-}$, $H{\cdot}CO_2^- \longrightarrow CO_2$, $CN^- \longrightarrow CNO^-$. Since the dark green precipitate of barium manganate can obscure the soluble purple MnO_4^- anion, direct titration is difficult and inaccurate, but back-titration of the excess of permanganate with sodium formate gave fairly satisfactory results. Stamm also developed a back-titration method depending on the fact that oxalic acid will reduce all manganese compounds to the manganous stage when the reaction mixtures are subsequently acidified. Stamm's procedures, however, have two major drawbacks: (1) oxidation of formate by alkaline permanganate is slow; mixtures cannot be heated without danger of further degradation of MnO_4^{2-} or of oxygen evolution, and catalysts, such as Ni^{2+}, Cu^{2+}, or Ag^+, though they accelerate the reaction, are themselves oxidised in part to higher oxides; (2) when alkaline permanganate is used for oxidation of organic compounds it often converts them, in part at least, into oxalate, thus vitiating the back-titration scheme.

We have now overcome these defects by making use of the rapid oxidation of the cyanide ion: $2MnO_4^- + CN^- + H_2O \longrightarrow 2MnO_4^{2-} + CNO^- + 2H^+$. After a chosen time interval we add a known excess of standard potassium cyanide to our oxidation mixtures and then filter them. The cyanide ion in the colourless filtrate can then be estimated by Liebig's method, and an accuracy of 1·5% is easily attainable, as test oxidations (see Table 3) show. Our results are collected together in Table 2.

Discussion.—Stamm (*loc. cit.*) and Duke (*J. Amer. Chem. Soc.*, 1948, **70**, 3975) suggested that the reversible reactions

$$MnO_4^- + H_2O \rightleftharpoons MnO_4^{2-} + H^+ + {\cdot}OH \text{ or } MnO_4^- + OH^- \rightleftharpoons MnO_4^{2-} + {\cdot}OH$$

occur rapidly in alkaline solutions of potassium permanganate, and this is supported by the fact that in alkaline solution radioactive exchange between the MnO_4^- and MnO_4^{2-} ions is immeasurably rapid (Libby, *ibid.*, 1940, **62**, 1930; Adamson, *J. Phys. Coll. Chem.*, 1951, **55**, 293). However, it does not accord with our experimental results given in Table 2, since diagnostic compounds such as ethyl ether and dioxan, which are rapidly oxidised by free hydroxyl radicals (Merz and Waters, *J.*, 1949, S15), are not attacked by alkaline permanganate. Again, *tert.*-butyl alcohol, and propionic, succinic, and adipic acid are attacked by hydroxyl radicals but not by permanganate, whilst conversely, acetone, malonic acid, and fumaric acid are rapidly attacked by alkaline permanganate but not by hydroxyl radicals, though, as Table 1 indicates, in some of these cases the differences in reactivity may be due to the very different acidities of the solutions used. We consider, therefore, that the oxidising actions of alkaline permanganate on both organic and inorganic compounds are directly due to the strong tendency of MnO_4^- anions to take one electron from any substrate capable of electron release (not hydrogen, H·, release), and it is significant that under our conditions no organic compound at once reduces permanganate beyond the manganate stage. Since the permanganate anion undergoes only a unit valency change, it follows that, unless permanganate oxidations are of second order with respect to MnO_4^-, the formation of transient organic free radicals should be expected. Unfortunately, permanganate so rapidly oxidises olefins that the usual test of induction of vinyl polymerisation cannot be applied.

The following deductions can be drawn about oxidations of organic groups:

(1) Saturated carboxylic acids in general are not attacked: this established the stability of the C–H and C–C links of paraffin chains. Malonic acid seems to be exceptional; it is oxidised to oxalate and carbon dioxide.

(2) Amongst alcohols and aldehydes, only the following reactions were found to be quantitative: $CH_3{\cdot}OH \longrightarrow CO_2 + 2H_2O$, $PhCH_2{\cdot}OH \longrightarrow PhCO_2H + H_2O$, $PhCHO \longrightarrow PhCO_2H$ (5·95, 3·96, and 1·95 equiv. of oxidiser used, respectively. Calc.: 6, 4, and 2). Ethanol, however, consumes 4·93 equiv. of oxidiser and so must be oxidised beyond the

TABLE 2. *Oxidations of organic compounds with cold alkaline permanganate.*

Compound	Concn.: g./l.	Concn.: 10^{-3}M	Time of reaction, min.	No. of tests	Equiv. of O used per mol.
Alcohols:					
$CH_3{\cdot}OH$	0·109	3·42	80	5	5·95 ± 0·07
$C_2H_5{\cdot}OH$	0·197	4·28	60	5	4·93 ± 0·05
$C_6H_5{\cdot}CH_2{\cdot}OH$	0·730	6·76	60	5	3·96 ± 0·10
*cyclo*Hexanol	0·193	1·93	40	5	8·71 ± 0·08
Pinacol hydrate	0·326	1·44	60	5	21·8 ± 0·4
Aldehydes:					
$C_6H_5{\cdot}CHO$	1·162	11·0	40	4	1·98 ± 0·04
$C_2H_5{\cdot}CHO$	0·506	8·69	40	4	2·41 ± 0·03
n-$C_3H_7{\cdot}CHO$	0·855	11·9	60	5	2·53 ± 0·03
Ketones:					
$C_6H_5{\cdot}CO{\cdot}CH_3$	0·338	2·82	90	6	7·94 ± 0·15
$CH_3{\cdot}CO{\cdot}CH_3$	0·081	1·40	40	3	12·1 ± 0·15
	0·107	1·85	90	4	12·05 ± 0·06
$C_2H_5{\cdot}CO{\cdot}CH_3$	0·238	3·31	60	4	10·8 ± 0·1
,, (½NaOH)	0·238	3·31	60	3	10·5 ± 0·15
*cyclo*Hexanone	0·291	2·97	40	4	7·09 ± 0·10
Unsaturated acids: *					
Cinnamic	0·382	2·58	45	4	7·95 ± 0·10
Crotonic	0·178	2·07	45	4	9·97 ± 0·10
Hex-2-enoic	0·249	2·18	60	4	9·82 ± 0·15
Substituted acids:					
Glycollic	0·347	4·57	60	4	3·96 ± 0·05
Lactic	—	2·52	60	4	10·7 ± 0·1
Malonic	0·330	3·18	60	4	5·99 ± 0·10
Amines:					
$CH_3{\cdot}NH_2$,HCl	0·443	6·56	60	4	2·7 ± 0·10
$(CH_3)_2NH$,HCl	0·552	6·77	60	4	6·9 ± 0·10
$(CH_3)_3N$,HCl	0·178	1·87	60	4	11·6 ± 0·07
N-Methylpiperidine	0·288	2·90	60	5	6·46 ± 0·05

* Maleic and fumaric acids were also examined, but the results are unreliable since they form insoluble barium salts; each used about 7 equiv. of permanganate.

TABLE 3. *Test oxidations of analytically pure reagents with alkaline permanganate.*

Compound	Concn., g./l.	Time of reaction, min.	$AgNO_3$, 10^{-3}M	Mean titres, ml.	No. of tests	Equiv. per mole: Found	Theory
KIO_3	2·1992	20	5·63	9·00	4	1·98	2
KIO_3	2·1992	135	5·63	8·95	3	1·98	2
KI	0·2081	60	5·37	4·65	4	7·95	8
$NaHCO_2$	0·6424	15	5·21	9·15	4	2·02	2
As_2O_3	1·0726	60	5·21	10·35	4	3·98	4

acetic acid stage, though this acid is quite stable to permanganate. The following reactions are possible: (*a*) $C_2H_5{\cdot}OH \longrightarrow H_2C_2O_4 + 2H_2O$ (10 equiv.) and (*b*) $C_2H_5{\cdot}OH \longrightarrow 2CO_2 + 3H_2O$ (12 equiv.), and both may be involved to some extent. Again, *cyclo*hexanol is oxidised beyond the stage of adipic acid, and lactic acid beyond pyruvic acid, though both these carboxylic acids resist attack. The oxidation of pinacol, too, is much more extensive than would be the case if it were converted *via* acetone into acetic acid and carbon dioxide, but in marked contrast *tert.*-butyl alcohol is not oxidised, and the slight oxidation of *tert.*-amyl alcohol may be due to an isomeric impurity.

This extensive oxidation of the group $\cdot CH_2{\cdot}CH(OH)\cdot$ is in accord with the oxidations of prop- and *n*-butyraldehyde (2·41 and 2·53 equiv. of oxidiser consumed) which degrade them below the stages of the corresponding carboxylic acids. Since the environment is strongly alkaline, we suggest that the oxidations of the aldehydes, and therefore of the alcohols too, proceed in part by way of the enols, RCH:CH·OH, which, like olefins, could be attacked at the C=C bond and so oxidised beyond the original C–O site.

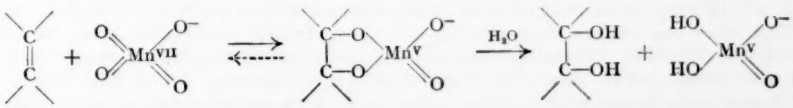
(3) In a similar way, aliphatic ketones are extensively degraded in strong alkali; *e.g.*, acetone, which is inert in neutral permanganate, consumes 12·1 equiv. in alkali, whereas even oxidation to acetic acid and carbon dioxide requires but 8 equiv. Stamm (*loc. cit.*) reported that acetone was degraded completely to carbon dioxide (16 equiv.) but we have been unable to confirm his results even after allowing excess of reagent to interact for as long as 90 minutes. The fact that the oxidation of acetophenone can be represented quantitatively by the equation $PhCO{\cdot}CH_3 \longrightarrow PhCO_2H + CO_2 + H_2O$ shows that an acetyl group can be oxidised completely if enolisation necessarily occurs to give $\cdot C(OH){:}CH_2$, but since carboxylic acids are not further degraded it follows that the oxidation of aliphatic ketones must occur by rapid progressive enolisation as each new carbonyl group is formed, thus:

$$RCO{\cdot}CH_2{\cdot}CH_2R' \xrightarrow{OH^-} RC(OH){:}CH{\cdot}CH_2R' \xrightarrow{MnO_4^-} RCO{\cdot}CO{\cdot}CH_2R' \longrightarrow RCO{\cdot}C(OH){:}CHR' \longrightarrow \text{etc.}$$

Since the anions of both oxalic and pyruvic acids resist attack, the 1 : 2-diketone stage formulated above seems to offer much more resistance to oxidation by C–C bond fission than to enolisation, and we therefore suggest that electron abstraction by MnO_4^- anions can easily take place from the anions of alcohols (or enols), but not from the more firmly bound electrons of carbonyl or carboxylate groups.

(4) Olefinic bonds are rapidly oxidised. The *cis*-glycol stage found under neutral conditions does not persist in strongly alkaline solutions and complete fission of the C=C group occurs. Thus the reaction $PhCH{:}CH{\cdot}CO_2H \longrightarrow PhCO_2H + HO_2C{\cdot}CO_2H$ is quantitative, though both crotonic and hex-2-enoic acid (9·97 and 9·85 equiv. of oxidiser) are oxidised well beyond the stage indicated by the equation $RCH{:}CHR' \longrightarrow RCO_2H + R'CO_2H$ (8 equiv.), so again the oxidation would seem to pass down a paraffin chain by way of a $\cdot CO{\cdot}CO\cdot$ group.

Boeseken (*Rec. Trav. chim.*, 1922, **41**, 199) suggested that the oxidation of olefins to *cis*-glycols by dilute, feebly alkaline, permanganate solutions occurred through the formation of a cyclic manganese derivative which subsequently hydrolysed:



This scheme is especially attractive since Criegee (*Annalen*, 1936, **522**, 75) has established that oxidations of olefins by osmium tetroxide take place by way of a structurally similar cyclic compound; however, with permanganate, it would require a valency change of two units at the manganese, and our quantitative results with cinnamic acid show that the permanganate anion is not degraded below the manganate stage in the presence of barium ions. For the cyclic scheme to be valid it would be necessary to assume (i) that an immediate reaction $MnO_4^- + MnO_4^{3-} \longrightarrow 2MnO_4^{2-}$ follows the hydrolysis of the cyclic complex before any Mn^V is further degraded to Mn^{IV}, and (ii) that the formation of the complex is so very much slower than its hydrolysis that enough MnO_4^- is always available to ensure that the reoxidation (i) of MnO_4^{3-} is quantitatively complete. These conditions appear to be so stringent that we think that it much more probable that the attack on the C=C bond requires 2 molecules of permanganate and that the organic compound is oxidised in two consecutive one-electron stages by way of a transient radical-ion.

(5) Amines, too, are oxidised, though not quantitatively, and since there are many reports of dealkylation by means of permanganate, it is probable that attack occurs vicinally to the nitrogen atom. Though the unshared electrons of amines are obvious initial points for electron abstraction, it is difficult to see from electronic considerations why $CH{-}\ddot{N}{<}^{C}_{C}$ should be so much more oxidisable than $CH{-}\ddot{\underset{\cdot\cdot}{O}}{-}C$ (as in ethers) though the basicity of amines is, after all, indicative of some tendency to electron release from the nitrogen. If attack by hydroxyl radicals were involved then again both amines and ethers should be attacked at CH groups in the α-position to the hetero-atom.

Experimental (Part I)

Titration Method.—Approx. 0·04M-potassium permanganate (20 ml.), 25% (w/v) sodium hydroxide solution (10 ml.), saturated barium nitrate solution (5 ml.), and distilled water (10 ml.) or substrate solution are pipetted into a 250-ml. conical flask in the order given, the mixture is shaken, and kept at room temperature for the required time (Tables 2 and 3). Approx. 0·02M-potassium cyanide (30 ml.) is then added, the mixture shaken, and the precipitate allowed to settle. A few drops of 10% potassium iodide are added, and the solution is filtered (No. 3 sintered-glass filter), the precipitate thoroughly washed with distilled water, and the combined filtrate titrated with 0·005M-silver nitrate (since $AgNO_3 \equiv 2KCN$ in Liebig's titration and $KCN \equiv 2KMnO_4$, M-silver nitrate is 4N with respect to the oxidation).

A blank titration is necessary because most samples of sodium hydroxide contain impurities which reduce a little alkaline permanganate. The amount of barium nitrate used is the minimum needed to ensure complete precipitation of the manganate: if too much is used, a troublesome barium carbonate precipitate is formed in the filtrate.

Tests (Table 3) with oxidisable inorganic compounds (compare Stamm, *loc. cit.*) show that in any given set of titrations concordance to 0·10 ml. can be attained and that the numbers of equivalents of oxygen used per mole are reliable to within ±1·5%. The calculated value is usually a little below the theoretical figure, probably on account of incomplete reaction at high dilution of the substrate.

Materials.—" AnalaR " potassium permanganate was dissolved in boiled-out distilled water, and the solution boiled for 30 minutes, cooled, and filtered. Laboratory reagent potassium cyanide in dilute solution gave a constant titre for at least 4—5 days; fresh solution was prepared every 2 days. Silver nitrate, sodium formate, potassium iodide, potassium iodate, and arsenious oxide were all freshly dried " AnalaR " reagents. Methanol was treated with iodine and sodium hydroxide to remove ethanol, fractionated, dried (K_2CO_3), and redistilled from magnesium; it had b. p. 65°. Ethanol, distilled from magnesium, had b. p. 78°. A solid specimen of *tert.*-butanol was distilled, and the distillate twice frozen, the crystals being kept; they had b. p. 81°. *tert.*-Amyl alcohol, dried (K_2CO_3) and fractionally distilled, had b. p. 102°. Benzyl alcohol, successively shaken, in ether, with potassium hydroxide and then sodium hydrogen sulphite solutions, dried, and fractionally distilled in a nitrogen atmosphere, had b. p. 97°/14 mm. *cyclo*Hexanol, fractionally frozen and then fractionated, had b. p. 160°.

Diethyl ether was shaken with aqueous sodium hydroxide containing silver oxide, then dried (Na) and distilled. Dioxan was refluxed with N-hydrochloric acid in a stream of air, then treated with caustic alkali, dried (Na), and distilled; it had b. p. 101°. Acetone and ethyl methyl ketone were shaken with aqueous sodium hydroxide containing silver oxide, then dried (K_2CO_3), and distilled. Prop- and but-aldehydes were dried ($MgSO_4$) and fractionated. Benzaldehyde was fractionated in a nitrogen atmosphere. Other liquids were dried and fractionally distilled. Solid compounds were crystallised to constant m. p. before use. *cyclo*-Hexanone was purified through the bisulphite compound.

Part II. Oxidations with Manganic Salts

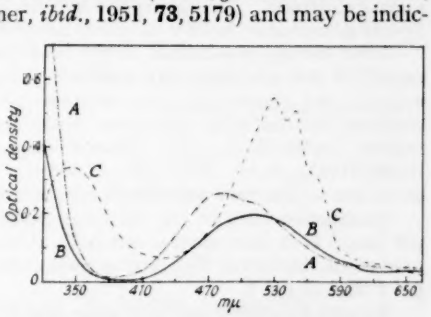
Most manganic salts are unstable in water, disproportionating, $2Mn^{3+} \rightleftharpoons Mn^{2+} + Mn^{4+}$, and depositing hydrated dioxide. For instance, Domange (*Bull. Soc. chim.*, 1939, **6**, 594) has shown that manganic sulphate is stable only in sulphuric acid of over 52% concentration: this is obviously unsuited for studies with organic compounds and so only qualitative tests have been made with it (see Table 1). Several manganic complexes of general formula $M_3(MnX_3)^{3-}$ (where M is a univalent cation and X a bivalent anion) are much more stable in water (cf. Taube, *Chem. Reviews*, 1952, **50**, 47), and we have found that the complex manganic pyrophosphate first described by Kolthoff and Watters (*loc. cit.*, 1943) can conveniently be used in the range pH 1—6 at temperatures up to 50° for quantitative kinetic work. Though it immediately decomposes in alkaline solutions, the salt, at pH 6·2, gives a dull red solution which is stable for at least 3 weeks at room temperature. On acidification the solution becomes bright red-violet owing to a change in the degree of ionisation of the pyrophosphate (Kolthoff and Watters, *loc. cit.*, 1948) and not owing to partial conversion into permanganate, since the absorption spectrum of the solution changes but slightly and shows no sign of the characteristic, very strong, absorption band of the MnO_4^- anion at 5300 Å (see Figure). From the acid solutions a red precipitate

of a manganic orthophosphate is eventually deposited, and evidently results from acid-catalysed hydrolysis of the pyrophosphate. Towards inorganic compounds, manganic pyrophosphate behaves as would be expected of a reagent with an oxidation–reduction potential, E_0, of 1·15 v. Table 1, however, shows that it is quite selective in its action upon organic compounds, but behaves similarly to, though much less vigorously than manganic sulphate (E_0 1·51 v), as would be expected of an easily dissociable complex (Taube, *loc. cit.*).

The selectivity of action of manganic salts upon organic compounds emphasises the extent to which oxidations effected by acid permanganate are due to manganese in a valency state higher than Mn^{3+}. The following features merit comment.

(1) Olefinic compounds such as maleic, fumaric, and cinnamic acid are not oxidised either by cold manganic sulphate or by manganic pyrophosphate at pH 1 and 50°. Acid permanganate at once attacks these compounds, but if a complexing agent is added, the characteristic red colour of Mn^{3+} is soon formed and persists for a considerable time.

(2) Monohydric alcohols also are not attacked by Mn^{3+}, in accordance with the conclusions of Merz, Stafford, and Waters (*loc. cit.*). In this respect Mn^{3+} resembles Ce^{4+} but not Co^{3+} (Bawn and White, *J.*, 1951, 343). However, 1 : 2-glycols and glycollic acid can be oxidised, and this selectivity again resembles that of ceric salts (Duke, *J. Amer. Chem. Soc.*, 1947, **69**, 2885; 1949, **71**, 2790; Duke and Bremer, *ibid.*, 1951, **73**, 5179) and may be indic-



Absorption Spectra of Manganic Pyrophosphate Solutions.

A, 0·00248M-*Manganic pyrophosphate solution*, pH 6·0.
B, 0·00248M-*Manganic pyrophosphate solution*, pH 1·44.
C, 0·000203M-$KMnO_4$.

ative of the formation of a cyclic intermediate. Other oxidisable compounds which may act by way of cyclic complexes are malonic and oxalic acids, and in the latter case there is very strong evidence that the breakdown of a manganioxalate complex is a rate-determining stage in the frequently studied permanganate–oxalic acid reaction (Malcolm and Noyes, *ibid.*, 1952, **74**, 2769, and earlier papers).

(3) Aldehydic compounds, with the conspicuous exceptions of formaldehyde, formic acid, and chloral, are oxidised rapidly by manganic sulphate, and at a measurable speed by manganic pyrophosphate solution. The oxidations of both propaldehyde and *n*-butaldehyde with manganic pyrophosphate have been followed kinetically at 37·3° and proved to be reactions of zero order with respect to the manganic compound, but of first order with respect to both aldehyde and hydrogen-ion concentration (at pH 1—2). When the manganic solution was in excess, propaldehyde consumed 4·15 equiv. and *n*-butaldehyde 3·90 equiv. per mole, so that, as in their oxidations by alkaline permanganate (Part I), they are degraded beyond the stage of the corresponding carboxylic acid. This evidence points to oxidation *via* the enol, the rate-determining stage being the slow acid catalysis of enolisation :

$$RCH_2{\cdot}CHO + H^+ \overset{\text{fast}}{\rightleftharpoons} RCH_2{\cdot}CH{:}O^+{\cdot}H \overset{\text{rate-determining}}{\longrightarrow} RCH{:}CH{\cdot}OH + H^+$$

and it is significant that the aldehydes cited above as being resistant to oxidation cannot form enols. Since olefins are not oxidised by Mn^{3+} it is not logical in this case to assign the oxidisability of the enols to the ease of electron release from C=C. Some metallic ions, such as Co^{3+}, can catalyse the autoxidation of aldehydes, and it has been suggested that this is due to the electron-transfer reaction $R{\cdot}CHO + Co^{3+} \longrightarrow R{\cdot}\dot{C}O + Co^{2+} + H^+$ which generates the acyl free radical $R{\cdot}\dot{C}O$ which rapidly combines with oxygen. How-

ever, a test with a differential manometer showed that manganic pyrophosphate did not accelerate the uptake of oxygen by aldehydes in aqueous solution.

Further knowledge of the mechanism of oxidation by manganic salts must therefore be sought by the study of other reactions which prove to be kinetically dependent upon manganese concentration.

Experimental (Part II)

Materials.—Manganic sulphate solutions were prepared as described by Ubbelohde (*loc. cit.*) and their oxidising power was tested qualitatively by the additions of excess of organic compounds at room temperature.

Sodium manganic pyrophosphate was prepared by Lingane and Karplus's method (*Ind. Eng. Chem. Anal.*, 1946, **18**, 191): Manganous sulphate solution (114 g. of "AnalaR" $MnSO_4,4H_2O$ per l.; 5 ml.) was mixed with sodium pyrophosphate solution (70 g. of "AnalaR" $Na_4P_2O_7,10H_2O$ per l.; 110 ml.), adjusted to pH 6 (glass-electrode titration) with 4N-sulphuric acid, and titrated electrometrically with potassium permanganate solution to the manganic end-point, a Cambridge Electrotitration apparatus being used. Larger batches of the manganic salt solution were then prepared in calculated volume as required. For quantitative work the reagent was estimated iodometrically. pH adjustment was made by addition of dilute sulphuric acid, and the final value was always checked against standard buffers by use of a glass electrode. The absorption spectra given in the figure were measured with a Beckman Spectrophotometer, a 12-v tungsten lamp source and a 1-cm. cell being used.

After storage of solutions at pH 1—2 for some hours a red precipitate was deposited, more rapidly if the solutions were warmed. This solid rapidly oxidised acidified potassium iodide solution and rapidly gave an orthophosphate reaction with ammonium molybdate reagent. Analyses for oxidising equivalent, total manganese, and total phosphorus indicate that it is mainly $NaMn(HPO_4)_2,H_2O$ [Found (mg.-atoms per g.): Mn, 3·40; P, 7·25. Calc. for $NaMn(HPO_4)_2,H_2O$: Mn, 3·47; P, 6·94]. A trihydrate (cf. Rosenheim, *Ber.*, 1915, **48**, 582) gives less satisfactory agreement, but the product is evidently impure.

Qualitative tests of the oxidising powers of manganic pyrophosphate solutions over the pH range 1—6 were carried out both at room temperature and up to 60°. In general, when oxidations did occur they had a measurable speed, and usually were much more obvious at pH 1 than at pH 6.

Kinetic measurements with prop- and *n*-but-aldehydes were made at 37·3°, freshly-prepared aldehyde solutions being used and manganic pyrophosphate solutions of checked pH which had been allowed to reach the thermostat temperature before being mixed. After measured time intervals, aliquot portions of the mixtures were added to potassium iodide solution, and the

Table 4. *Oxidations of aldehydes with manganic pyrophosphate solution: evidence for zero order of reaction with respect to* Mn^{3+}.

A. Propaldehyde, 0·112M, at pH 1·33.

Initial Mn^{3+}, 1·90 × 10^{-2}N.			Initial Mn^{3+}, 0·95 × 10^{-2}N.		
Time, min.	Δ, ml.*	Diff.	Time, min.	Δ, ml.	Diff.
0	0		0	0	
12	1·10	0·75	10	0·80	0·65
24	1·85	0·85	20	1·45	0·65
36	2·70	0·85	30	2·10	0·65
48	3·55	0·75	40	2·75	0·60
60	4·30	0·75	50	3·35	0·80
72	5·05	0·75	60	4·15	0·40
84	5·80		70	4·55	
Mean Δ/min., 0·067 ml.			Mean Δ/min., 0·063 ml.		

B. *n*-Butaldehyde, 0·0679M at pH 1·30.

Initial Mn^{3+}, 1·84 × 10^{-2}N; mean Δ/min., 0·043 ml. (± 0·015) †
Initial Mn^{3+}, 1·38 × 10^{-2}N; mean Δ/min., 0·041 ml. (±0·011)

C. *n*-Butaldehyde, 0·0733N at pH 1·17.

Initial Mn^{3+}, 1·84 × 10^{-2}N; mean Δ/min., 0·057 ml. (±0·010)
Initial Mn^{3+}, 0·97 × 10^{-2}N; mean Δ/min., 0·058 ml. (±0·010)

The mean titre changes given above have been taken from 8 or 9 measurements, which in each series fall smoothly on a linear plot.

* Δ = Decrease in titre (here and in Table 5).

† These errors are not those of the mean, but the averaged error of any one reading (*i.e.*, ±0·1 ml. when titrations are taken at 10-min. intervals). In all cases the error of the mean is no more than 0·002 ml.

liberated iodine was estimated by means of standard sodium thiosulphate. Table 4 shows that the reactions are of zero order with respect to the manganic salt, and Table 5 shows that they are first-order processes with respect to both the aldehyde and the hydrogen ion.

TABLE 5. *Oxidations of aldehydes with manganic pyrophosphate solution.*

A. Evidence for first order of reaction with respect to aldehyde.

Initial Mn^{3+}, 1.87×10^{-2}N; pH 1·35.

Molality of C_2H_5·CHO	0·112	0·168	0·090
Mean time, min., for $\Delta = 2.00$ ml.	33·8	22·5	41·5
Product (Molality × Time)	3·79	3·78	3·74

Initial Mn^{+3}, 1.84×10^{-3}N.

	At pH 1·30		At pH 1·17	
Molality of C_3H_7·CHO	0·0679	0·0509	0·0733	0·0367
Mean time, min., for $\Delta = 2.0$ ml.	48·5	65·5	34·8	71·5
Product (Molality × Time)	3·29	3·33	2·55	2·62

B. Evidence for first order of reaction with respect to $[H^+]$.

pH	$[H^+]$	Mean time, min., for $\Delta = 2.00$ ml.	$[H^+] \times$ (Time)	pH	$[H^+]$	Mean time, min., for $\Delta = 2.00$ ml.	$[H^+] \times$ (Time)
		0·0576M-C_2H_5·CHO; initial Mn^{3+}, 1.90×10^{-2}N.					
1·34	0·0457	55	2·51	1·68	0·0209	117·5	2·46
		0·0679M-*n*-C_3H_7·CHO; initial Mn^{3+}, 1.84×10^{-3}N.					
1·30	0·0507	48·5	2·42	1·49	0·0324	74·7	2·42
		0·0733M-*n*-C_3H_7·CHO; initial Mn^{3+}, 1.84×10^{-3}N.					
1·17	0·0676	34·8	2·35	1·33	0·0468	54·0	2·52

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89. *The Synthesis and the Physical Properties of Alkylnaphthalenes.*

By D. G. ANDERSON, J. C. SMITH, and (in part) R. J. RALLINGS.

Earlier syntheses have been extended up to 1- and 2-*n*-hexadecylnaphthalene. A summary of the physical properties of 1- and 2-alkylnaphthalenes is given and the changes from aromatic to aliphatic characteristics are shown.

As now all the α- and β-mono-*n*-alkylnaphthalenes up to the hexadecylnaphthalenes have been studied in this laboratory (Morrell, Pickering, and Smith, *J. Inst. Petrol.*, 1948, **34**, 677; Bailey, Pickering, and Smith, *ibid.*, 1949, **35**, 103; Bannister and Elsner, *J.*, 1951, 1055; Anderson and Smith, *J. Inst. Petrol.*, 1952, **38**, 415) it is opportune to generalise on the methods of preparation suitable for each series and to examine the accumulated data on physical properties.

For the α-substituted naphthalenes (1-1′-naphthylalkanes), the size of the alkyl chain determines which method of preparation is the most appropriate. 1-Methylnaphthalene is obtained pure from commercial (60%) 1-methylnaphthalene by the sulphonation–desulphonation process (Coulson, *J. Soc. Chem. Ind.*, 1943, **62**, 177; Morrell, Pickering, and Smith, *loc. cit.*). Soffer and Stewart's recent observation (*J. Amer. Chem. Soc.*, 1952, **74**, 567) that the trinitrobenzene complex of 1-methylnaphthalene can be obtained pure from a mixture with the 2-compound (where the picrate method fails) should make the chloromethylnaphthalene route (Morrell, Pickering, and Smith, *ibid.*, p. 680) suitable for small quantites.

1-Ethyl- and 1-propylnaphthalene were prepared through the ketones: Friedel–Crafts reactions with acetyl or propionyl chloride yielded sufficient alkyl 1-naphthyl ketone to make practicable a separation of the picrates. By the Wurtz–Fittig reaction between 1-bromonaphthalene and 1-bromo-butane, -pentane, or -hexane reasonable yields of easily purified products were obtained. From 1-heptyl- to 1-hexadecyl-naphthalene, the condensation between 1-naphthylmagnesium bromide and the alkyl cyanide has given good results (Bannister and Elsner, *loc. cit.*; cf. Nunn and Henze, *J. Org. Chem.*, 1947,

12, 540). Condensation of α-tetralone with Grignard reagents to yield the alcohol and then the olefin was used in two cases (Bailey, Pickering, and Smith; Anderson and Smith, *locc. cit.*). Because of the possibility of freeing them completely from isomerides 1-bromonaphthalene and 1-tetralone are much-preferred starting materials. The suitability of 1-naphthaldehyde is at present being investigated.

For the β-compounds (1-2′-naphthylalkanes) the Friedel–Crafts reaction between an acid chloride and naphthalene (or tetrahydronaphthalene) in nitrobenzene was always used (Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1945, **12**, 307) as the β-ketone was then readily obtained pure and in high yield. Wherever possible the same specimen of alkyl derivative (bromide or cyanide) was used for the preparation of each of the pair of hydrocarbons, *e.g.*, *n*-tridecanonitrile with 1-naphthylmagnesium bromide for the *n*-dodecyl

FIG. 1.
M. p.s of alkylnaphthalenes.

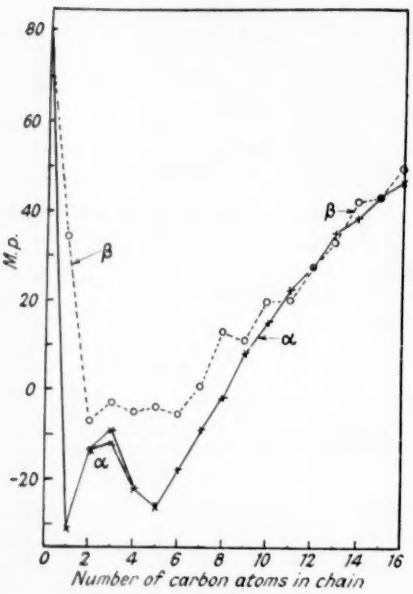
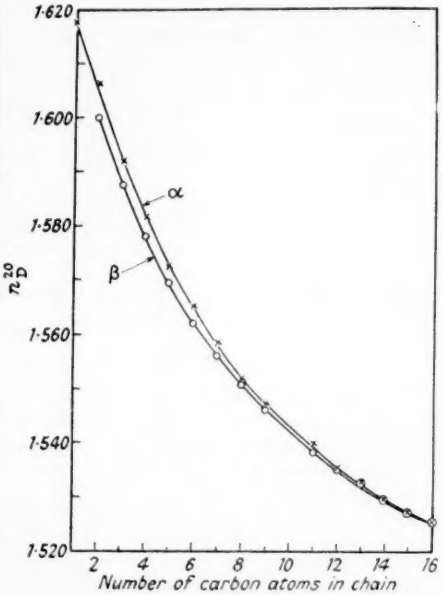


FIG. 2.
n_D^{20} *of alkylnaphthalenes.*



1-naphthyl ketone and, after conversion into *n*-tridecanoyl chloride, with naphthalene for the 2-naphthyl ketone.

In most cases previous work left no doubt as to the structure of the ketone or hydrocarbon synthesised, but in some compounds the orientation of the side-chain was established by oxidation. For example, ethyl 1-naphthyl ketone, oxidised with selenium dioxide in dioxan, gave a crude 1 : 2-diketone which, on treatment with alkaline hydrogen peroxide solution, yielded 1-naphthoic acid (Morrell, Pickering, and Smith, *loc. cit.*). This method has been applied also to *n*-amyl 2-naphthyl ketone (Bailey, Pickering, and Smith, *loc. cit.*) and to 1 : 4-di-(5 : 6 : 7 : 8-tetrahydro-2-naphthoyl)butane (Bannister and Elsner, *loc. cit.*).

A satisfactory method of orientating the side-chains of the hydrocarbons by oxidation to 1- or 2-naphthoic acid was developed for 2-*n*-butylnaphthalene. The action of *N*-bromosuccinimide, followed by alkali, on 2-butylnaphthalene gave an olefin which was readily oxidised with permanganate in acetone to 2-naphthoic acid (Pickering and Smith, *Rec. Trav. chim.*, 1950, **69**, 535; cf. Buu-Hoï and Lecocq, *J.*, 1946, 830).

After the intermediates had been carefully purified they were converted into the hydrocarbons which were fractionally distilled, and then crystallised to constant m. p. and

refractive index. (Owing to the difficulty of measuring refractive indices at 30—50° accuracy beyond the third place of decimals is not claimed in the values recorded.)

From an inspection of atomic models of the alkylnaphthalenes it appears that the 2-naphthyl isomerides should be less dense than the 1-isomerides, if a freely rotating methylene chain is assumed. In Table 1 the densities recorded all agree with this view. The 2-alkylnaphthalenes have also the lower refractive indices.

Besides this interesting difference between 1- and 2-substituted naphthalenes there is also the gradual change of physical properties (in both the series) with increasing length of paraffin chain. Plotting the refractive index (or the density) against the number of carbon atoms in the paraffin chain gives a smooth curve showing, with increasing molecular weight, a gradual approach to aliphatic values (see Fig. 2): the denser, more highly refracting, aromatic hydrocarbon is changing to the lighter, less refracting, aliphatic type.

For the first six pairs of homologues (1- and 2-isomerides) the boiling points could be measured at atmospheric pressures. The measurements, all made on the same day by distillation from the same apparatus, show that 1-methyl- and 1-ethyl-naphthalene have higher boiling points than the 2-isomerides, but that 2-propyl-, 2-butyl-, 2-pentyl-, and 2-hexyl-naphthalene are higher-boiling than the 1-isomerides. This crossing of the b. p.–C_n curves at C_3 is surprising (Bailey, Pickering, and Smith, *loc. cit.*). Higher in the series the boiling points listed (Table 1) are recorded during distillation *in vacuo* and are not sufficiently accurate to allow comparison.

TABLE 1.

	1-Alkylnaphthalene				2-Alkylnaphthalene			
Alkyl	B. p./mm.†	M. p.	n_D^{20}	d_4^{20}	B. p./mm.†	M. p.	n_D^{20}	d_4^{20}
Methyl	244·5°	−31°	1·6174	1·020	241°	34·2°	—	—
Ethyl	259	−13·5	1·6062	1·008	258	−7	1·5999	0·992
Propyl	272·5	−12, −9	1·5923	0·990	273·5	−3	1·5872	0·977
Butyl	289	−22	1·5811	0·977	292	−5	1·5776	0·966
Pentyl	307	−26	1·5728	0·966	310	−4	1·5694	0·956
Hexyl	322	−18	1·5652	0·958	323·5	−5·5	1·5621	0·948
Heptyl	141/0·5	−9	1·5583	0·9500	146/0·5	0·6	1·5565	0·9407
Octyl *	170/4	−2	1·5510	—	—	13	1·5511	—
Nonyl	138/0·05	8	1·5472	0·9367	139/0·08	11	1·5460	0·9304
Decyl *	200/4	15	1·5448	—	—	19·6	1·5440	—
Undecyl	145/0·01	22·4	1·5394	0·9280	151/0·01	20	1·5383	0·9220
Dodecyl	193/0·5	27·5	1·5348	—	—	27·0	1·5344	0·918
Tridecyl	198/0·5	35	1·5328	—	195/0·5	33	1·5325	—
Tetradecyl ...	204/0·7	38·5	1·5298	—	195/0·15	42	1·5296	—
Pentadecyl ...	213/0·5	43	1·5273	—	220/0·5	43	1·5271	—
Hexadecyl ...	223/0·5	46·5	1·5251	—	210/0·05	49·5	1·5249	—

* Bannister and Elsner, *loc. cit.*

† 760 mm. unless otherwise stated.

TABLE 2. n-*Alkyl naphthyl ketones.*

C atoms in alkyl (Me = 1)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M. p., 1-naphthyl:	10°	—	—	—	−12°	—	−3°	−8°	10°	—	26°	28°	39°	41°	46°
,, , 2-naphthyl:	53°	59°	53°	54°	68°	60°	58°	57°	52°	47°	47°	51°	55°	61°	62°

Melting points, being properties of the solid state, show less regularity (Fig. 1). After the initial drop from naphthalene (m. p. 80°) to 1- (m. p. −31°) and 2-methylnaphthalene (+34°; cf. benzene 5·5°, and toluene −91°) there is a surprisingly small variation up to the hexylnaphthalenes. Thereafter the aliphatic character begins to assert itself and the two series show rising melting points fitting on " mildly zig-zag curves " which cross and re-cross. It is well known that for nearly all naphthalene derivatives the 2-substituted isomeride is higher-melting (often 50° higher) than the 1-isomeride. With the *n*-alkylnaphthalenes the rule applies up to the decanes; but the undecylnaphthalenes, with more " aliphatic " than " aromatic " carbon atoms provide the first instance of a lower-melting 2-isomeride (1-, m. p. 22°; 2-, m. p. 20°).

Data on the melting points of *n*-alkyl naphthyl ketones are not complete, but the values listed in Table 2 (taken from the naphthalene literature already referred to) give m. p–C_n curves similar to those for the hydrocarbons. There is a maximum difference between the

1- and the 2-isomeride when the side-chain has 6 carbon atoms. After the dodecanoylnaphthalenes the m. p. curves are close and approximately parallel.

The infra-red and ultra-violet spectra of the two series of hydrocarbons have been measured in several laboratories and recorded earlier. Data now given are for only those hydrocarbons described in this paper.

Bailey, Pickering, and Smith (*loc. cit.*) pointed out that the alkylnaphthalenes formed complexes with the usual polynitroaromatic compounds only up to the hexylnaphthalenes. But even the *s*-trinitrobenzene complexes of the hexylnaphthalenes decomposed near their m. p.s; the picrates and styphnates could not be isolated.

Alkyl 2-naphthyl ketones form the usual ketonic derivatives (semicarbazones, oximes, etc.) though with decreasing activity as the length of the paraffin chain increases. From the first two or three *n*-alkyl 1-naphthyl ketones derivatives can be obtained slowly and with difficulty: higher ketones fail to give ketonic reactions except under extreme conditions.

Experimental

Attention to the prescribed detail is essential for the yields and purities recorded.

1-*Tridecylnaphthalene* (1-1'-*Naphthyltridecane*).—*Dodecan*-1-*ol*. Commercial dodecyl alcohol (m. p. 23°) gave on distillation at 140—145°/12 mm. 5 fractions, ranging from m. p. 22·8°, n_D^{25} 1·4404, to m. p. 23·5°, n_D^{25} 1·4409; the residue melted at 22·9°. Crystallisation of the purer fractions from acetone gave a final product of f. p. 23·90°, m. p. 23·95°, n_D^{25} 1·4410. Verkade and Coops (*Rec. Trav. chim.*, 1927, **46**, 903) give f. p. 23·8°, b. p. 130·3°/7 mm. 1-Bromododecane (90% yield by the procedure of *Org. Synth.*, Coll. Vol. I, 1941, pp. 29, 35) had b. p. 150—152°/18 mm., and n_D^{20} 1·4580—1·4584, n_D^{25} 1·4560—1·4564, throughout the distillation. Heston, Hennethy, and Smyth (*J. Amer. Chem. Soc.*, 1950, **72**, 2071) give n_D^{25} 1·45637.

Tridecanonitrile. The bromide (157 g.; n_D^{25} 1·4563), potassium cyanide (60 g.; AnalaR), water (70 c.c.), and ethanol (160 c.c.) were heated under reflux for 6 hours. After addition of more potassium cyanide (20 g.), water (30 c.c.), and ethanol (30 c.c.) the mixture was further heated for 48 hours to complete the reaction: the resulting crude nitrile (114 g., 92%) was free from halogen. After distillation at 120°/1 mm. the colourless product crystallised from ethanol at −30° and then melted at +9·6° (thermometer in the liquid) and boiled at 113°/0·2 mm.; n_D^{20} was 1·4388. All the nitrile was systematically crystallised to yield a stock of pure tridecanonitrile, m. p. 9·65°. This substance has not previously been described as a solid. The liquid boils at 275°/760 mm. (Lutz, *Ber.*, 1886, **19**, 1438). Daragan (*Bull. Soc. chim. Belg.*, 1935, **44**, 597) gives n_D^{20} 1·43867.

n-*Dodecyl* 1-*naphthyl ketone*. Bromonaphthalene (m. p. 5°), crystallised from ethanol at −18°, yielded a product of m. p. 6·15° (thermometer in the liquid). Recrystallisation gave pure 1-bromonaphthalene, m. p. 6·17°. Jones and Lapworth (*J.*, 1914, **105**, 1804) give m. p. 6·2°.

To a solution of 1-naphthylmagnesium bromide (from magnesium, 5·34 g., 0·22 g.-atom; 1-bromonaphthalene, 41·4 g., 0·20 mole; ether, 90 c.c.) was added with stirring tridecanonitrile (31 g., 0·16 mole; m. p. 9·65°) in ether (60 c.c.) during 1 hour while the mixture was refluxing on a hot-plate; heating was continued for 18 hours. There resulted a clear, brown solution and a little unchanged magnesium. After decomposition with water and acid the mixture yielded 4 g. of naphthalene and then 47 g. of a fraction (92%), b. p. 210—220°/0·1 mm., m. p. 26—27°. This *ketone* crystallised easily from acetone at −10°. Systematic crystallisation gave 42·5 g. (82%, calc. on the nitrile) of pure ketone, m. p. 29·25° (thermometer in the liquid), 30—31° (capillary tube), $n_D^{34\cdot5}$ 1·5367, $n_D^{29\cdot5}$ 1·5386, dn/dt 38 × 10^{-5}, n_D^{20} (calc.) 1·5422 (Found: C, 85·2; H, 10·1. $C_{23}H_{38}O$ requires C, 85·2; H, 9·9%). In common with other ketones of this type the substance failed to form carbonyl derivatives.

1-*Tridecylnaphthalene*. The ketone (31·9 g.; m. p. 29·2°) and copper chromite catalyst (8 g.) were stirred with hydrogen (max. pressure 160 atms.) at 200—230° for 4 hours and then for 15 minutes at 250°. After cooling and separation from the catalyst with the aid of ether the reduction product (27 g., 90%) boiled at 170—180°/0·05 mm. and had n_D^{20} 1·5028. This low refractive index indicated nuclear reduction, and the specimen was therefore dehydrogenated by heating it with palladium–charcoal (9 g. of hydrocarbon to 0·5 g. of catalyst). Evolution of hydrogen began at 200° and the temperature was gradually raised to 280° during 4 hours. In the presence of a slow stream of nitrogen the melt was heated for 10 minutes to 300°. The product (8·3 g.; b. p. 185°/0·1 mm.) froze at 33·2° and crystallised from acetone (50 c.c.) in ice-

water, melting at 34·5° (capillary tube); it had $n_D^{29·5}$ 1·5293, n_D^{20} (calc.) 1·5329. After being stirred with sodium at 170—200° for ½ hour in nitrogen, and then crystallised from acetone it had m. p. 34·5—35°, $n_D^{29·5}$ 1·5291 (Found: C, 88·8; H, 11·1. Calc. for $C_{23}H_{34}$: C, 89·0; H, 11·0%). Luther and Wächter (*Ber.*, 1949, **82**, 161) give n_D^{20} 1·5226 for their (liquid) specimen. An earlier preparation of the hydrocarbon had given n_D^{49} 1·5218, $n_D^{39·5}$ 1·5255, $n_D^{29·5}$ 1·5293, so $dn/dt = 38 \times 10^{-5}$, and, for the pure specimen above, n_D^{20} (calc.) 1·5328.

2-*Tridecylnaphthalene.*—n-*Dodecyl* 2′-*naphthyl ketone.* n-Tridecanonitrile (49 g.; m. p. 9·65°), potassium hydroxide (40 g.), water (40 c.c.), and ethanol (200 c.c.), when heated for 48 hours under reflux, yielded 53 g. of solid acid. Fractional distillation (with a short column) at 120—128°/0·01 mm. gave 6 g. of m. p. 40·3°, 25 g. of m. p. 41·5°, and 20 g. of m. p. 41·7°. Systematic crystallisation from light petroleum (b. p. 40—60°) brought all fractions to m. p. 41·65—41·70° and, from the mother-liquor, unchanged nitrile was recovered. Garner, Madden, and Rushbrooke (*J.*, 1926, 2491) give f. p. 41·1°.

The acid chloride, obtained in 80% yield by the action of purified thionyl chloride (2 mols. : 1 mol. of acid), boiled at 175°/30 mm., 156—158°/11 mm.

To a solution of pure naphthalene (6·3 g., 1·5 mols.) and tridecanoyl chloride (8·9 g., 1 mol.) in dry, distilled nitrobenzene, powdered aluminium chloride (5·5 g., 1·1 mols.) was gradually added during 0·5 hour, with stirring at <0°. After a further 0·5 hour's stirring the red mixture was left at 20° for 22 hours. Working up in the usual way (excess of naphthalene distilled over with the nitrobenzene) gave a yellow *ketone*, 210—220°/0·2 mm., f. p. 51° (11·7 g., 95%; 91% in another experiment). Crystallisation of 21·7 g. from alcohol and then from acetone gave 15·3 g. of m. p. 54° (capillary tube) (Found: C, 85·2; H, 9·8%). On evaporation of the mother-liquors 3 crops of crystals were obtained, all melting below 30° and containing, presumably, some of the isomeric 1′-naphthyl ketone, a little of which is formed even when nitrobenzene is used as the solvent for the Friedel–Crafts reaction. Ketone of m. p. 54° yielded a 2 : 4-*dinitrophenylhydrazone* (orange-red needles from ethyl acetate), m. p. 122° (Found: N, 11·1. $C_{29}H_{36}O_4N_4$ requires N, 11·3%).

Following the procedure of Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) the ketone (12 g.) in 2-2′-hydroxyethoxyethanol (30 c.c.) was added to a solution of sodium (3·0 g.) in this glycol (30 c.c.) and hydrazine hydrate (6·0 c.c. of 90%). After the mixture had been heated for 6 hours the condenser was removed and steam allowed to escape. When the temperature of the liquid reached 230° an air-condenser was fitted and refluxing continued for 18 hours. After an oil, b. p. 90—190°/0·1 mm. and smelling of burnt sugar, had distilled, the main product, b. p. 190—195°/0·1 mm., was obtained as a yellow oil (10·0 g., 87%). When the colour had been removed by passage in light petroleum through alumina, the recovered hydrocarbon was crystallised from acetone to the constant m. p. 33° and $n_D^{29·5}$ 1·5290 (supercooled), n_D^{20} (calc.) 1·5326.

A second, similar preparation gave a product (after treatment with alumina) of m. p. 27—30° with a high refractive index, n_D^{27} 1·5325, n_D^{20} (calc.) 1·5353, and setting to a soft, curdy mass. It seemed that unchanged ketone was present. Fractional distillation, with rejection of the higher-boiling fractions, followed by heating with sodium at 150—200°, gave a product of m. p. 32—33°, $n_D^{24·7}$ 1·5313, n_D^{20} (calc.) 1·5332. Crystallisation from acetone gave a *hydrocarbon* of m. p. 32·5—33, $n_D^{29·5}$ 1·5289, n_D^{20} (calc.) 1·5325, unchanged by further treatment with sodium and recrystallisation (Found: C, 88·8; H, 10·8. $C_{23}H_{34}$ requires C, 89·0; H 11·0%).

1-*Alkylnaphthalenes.*—These were all obtained in 80—90% yield by reduction of the ketones with copper chromite and hydrogen at 200—250°/150—200 atm., followed by dehydrogenation of the products as described in the preparation of 1-tridecylnaphthalene, and were crystallised from acetone to constant m. p.: 1-Dodecylnaphthalene, b. p. 193°/0·5 mm., m. p. 27·5° (capillary tube), n_D^{20} 1·5348 (super-cooled), n_D^{49} 1·5235, $n_D^{39·5}$ 1·5272, $n_D^{29·5}$ 1·5309, dn/dt 38 × 10^{-5}, n_D^{20} (calc.) 1·5346 (Buu-Hoï and Cagniant, *loc. cit.*, give m. p. 26·5°); 1-*tetradecylnaphthalene*, b. p. 204/0·7 mm., needles, m. p. 38·5°, dn/dt 39 × 10^{-5}, $n_D^{40·2}$ 1·5220, n_D^{20} (calc.) 1·5298 (Found: C, 88·9; H, 11·3. $C_{24}H_{36}$ requires C, 88·9; H, 11·1%); 1-*pentadecylnaphthalene*, b. p. 213°/0·5 mm., m. p. 42·5—43°, $n_D^{49·5}$ 1·5157, $n_D^{39·5}$ 1·5197, dn/dt 40 × 10^{-5}, n_D^{20} (calc.) 1·5273 (Found: C, 88·7; H, 11·2. $C_{25}H_{38}$ requires C, 88·8; H, 11·2%); 1-hexadecylnaphthalene, b. p. 223°/0·5 mm., m. p. 46—47° (Luther and Wächter, *loc. cit.*, give m. p. 37°), $n_D^{49·5}$ 1·5139, $n_D^{39·5}$ 1·5177, dn/dt 38 × 10^{-5}, n_D^{20} (calc.) 1·5251 (Found: C, 88·6; H, 11·4. Calc. for $C_{26}H_{40}$: C, 88·6; H, 11·4%).

n-*Alkyl* 1-*Naphthyl Ketones.*—These were prepared by methods similar to that for *n*-dodecyl 1-naphthyl ketone: 1-naphthyl undecyl ketone, b. p. 190°/1 mm., m. p. 26° [from 1-naphthylmagnesium bromide and pure dodecanonitrile, n_D^{20} 1·4360 (from dodecanoic acid, m. p. 43°);

Bannister and Elsner, *loc. cit.*, give, for the ketone, b. p. 234—236°/6 mm., m. p. 26·8°]; 1-*naphthyl* n-*tridecyl ketone*, b. p. 243°/1 mm., m. p. 39° [from myristonitrile, m. p. 19°, n_D^{20} 1·4411 (Daragan, *loc. cit.*, gives n_D^{20} 1·44126 for the nitrile; Dorinson and Ralston, *J. Amer. Chem. Soc.*, 1944, **66**, 361, give n_D^{20} 1·4410, m. p. 19·25°)] (Found: C, 85·1; H, 10·1. $C_{24}H_{34}O$ requires C, 85·2; H, 10·1%); 1-naphthyl *n*-pentadecyl ketone [from palmitonitrile, m. p. 31° (from palmitic acid, m. p. 63°) (Dorinson and Ralston, *loc. cit.*, give m. p. 31·40° for the nitrile)], b. p. 257°/1 mm., m. p. 48° (Found: C, 85·5; H, 10·4. Calc. for $C_{26}H_{38}O$: C, 85·2; H, 10·4%) (Ryan and Nolan, *Proc. Roy. Irish Acad.*, 1913, **30**, *B*, 1, give m. p. 48°).

1-*Naphthyl* n-*tetradecyl ketone*. Tetradecyl alcohol, m. p. 38°, was converted into the bromide, b. p. 167—169°/18 mm., n_D^{20} 1·4575, and this into the nitrile, b. p. 112°/0·5 mm., n_D^{25} 1·4413. Dorinson and Ralston (*loc. cit.*) give n_D^{25} 1·4413 for pentadecanonitrile. With 1-naphthylmagnesium bromide the nitrile yielded the *ketone*, b. p. 250°/1 mm., m. p. 41° (Found: C, 85·1; H, 10·3. $C_{25}H_{36}O$ requires C, 85·2; H, 10·2%).

2-*Alkylnaphthalenes*.—2-Dodecylnaphthalene was kindly supplied by Dr. S. L. Langedijk of the Koninklijke/Shell-Laboratorium, Amsterdam. The remaining 2-alkylnaphthalenes were prepared as follows:

2-*Tetradecylnaphthalene*. Purified tetrahydronaphthalene, tetradecanoyl chloride (from myristic acid, m. p. 54°), nitrobenzene, and aluminium chloride gave 2-(5 : 6 : 7 : 8-tetrahydronaphthyl) *n*-tridecyl ketone, b. p. 225°/0·5 mm., which, crystallised from acetone, melted at 36° (Kölbel and Fritsch, *Brennstoff-Chemie*, 1949, **30**, 73, give m. p. 36·5—36·8°). The 2 : 4-*dinitrophenylhydrazone*, red plates from alcohol, melted at 97° (Found: N, 10·6. $C_{30}H_{42}O_4N_4$ requires N, 10·7%). The crude product from the Huang-Minlon reduction was dehydrogenated (Pd–C at 280°) to give the alkylnaphthalene, b. p. 195°/0·15 mm. Crystallised twice from acetone it melted at 41·5—42·5° (Found: C, 88·8; H, 11·2. Calc. for $C_{24}H_{36}$: C, 88·9; H, 11·1%). Kölbel and Fritsch (*loc. cit.*) give m. p. 21·5°.

2-*Pentadecylnaphthalene*. Pentadecanonitrile, n_D^{25} 1·4413, was hydrolysed to pentadecanoic acid, m. p. 53—54° (lit., m. p. 53—54°). The acid chloride, b. p. 151°/5 mm., condensed with naphthalene in nitrobenzene in presence of aluminium chloride, yielded 2-*naphthyl tetradecyl ketone*, b. p. 230°/1 mm., m. p. 61° (from acetone) (Found: C, 85·0; H, 10·1. $C_{25}H_{36}O$ requires C, 85·2; H, 10·2%). The 2 : 4-*dinitrophenylhydrazone*, red needles from ethyl acetate, melted at 120—121° (Found: N, 10·2. $C_{31}H_{40}O_4N_4$ requires N, 10·5%). By Huang-Minlon reduction,

Infra-red spectra (15—6 μ).

1-Alkylnaphthalenes. Frequency (cm.$^{-1}$): liquid						2-Alkylnaphthalenes. Frequency (cm.$^{-1}$): liquid					
$C_{22}H_{32}$	$C_{23}H_{34}$	$C_{24}H_{36}$	$C_{25}H_{38}$	$C_{26}H_{40}$		$C_{22}H_{32}$	$C_{23}H_{34}$	$C_{24}H_{36}$	$C_{25}H_{38}$	$C_{26}H_{40}$	
691	690	691	691	690	w	720	720	720	720	720	s
721	721	721	721	721	s	744	744	744	744	744	vs
729	729	729	729	729	sh	815	815	815	813	813	vs
777	777	777	777	777	vs	853	854	853	852	852	s
792	792	792	792	792	vs	890	890	890	890	889	s
858	858	857	857	857	m	945	946	946	945	945	m
889	889	—	—	—	w	957	958	958	957	959	m
900	900	—	—	—	w	1018	1020	1019	1019	1019	m
948	948	947	948	947	m	1127	1127	1127	1127	1128	m
966	966	966	966	965	m	1145	1144	1145	1144	1142	w
1016	1017	1015	1015	1016	m	1155	1156	1156	1154	1154	w
1025	1026	1025	1026	1026	sh	1169	1171	1171	1171	1171	w
1080	1080	1079	1078	1080	m	1210	1212	1210	1210	1210	w
1116	1116	1117	1116	1115	w	1243	1243	1240	1240	1241	w
1123	1123	1123	1122	1125	w	1270	1270	1268	1269	1269	m
1144	1145	1142	1142	1142	w	1304	1304	1304	1304	1304	w
1166	1166	1164	1165	1164	m	1370	1370	1365	1365	1365	m
1217	1217	1217	1217	1218	w	1466	1466	1466	1466	1466	s
1241	1242	1240	1239	1239	w	1508	1508	1508	1508	1508	m
1260	1262	1260	1261	1260	m	1605	1605	1610	1608	1610	m
1300	1300	1300	1300	1300	w	1635	1635	1635	1635	1635	m
1358	1358	1358	1358	1358	w						
1376	1376	1376	1376	1376	m						
1396	1396	1396	1396	1396	m						
1466	1466	1466	1466	1466	s						
1508	1508	1508	1508	1508	m						
1600	1600	1600	1600	1600	m						

s = Strong; vs = very strong; m = medium; w = weak; sh = shoulder.

at 240° for 16 hours, the ketone yielded a *hydrocarbon*, b. p. 220°/0·5 mm. Three crystallisations from acetone gave a product of sharp m. p. 43° (Found: C, 88·6; H, 11·1. $C_{25}H_{38}$ requires C, 88·8; H, 11·2%).

2-*Hexadecylnaphthalene*. (*a*) *n*-Pentadecyl 2-(5 : 6 : 7 : 8-tetrahydronaphthyl) ketone was prepared from tetrahydronaphthalene, palmitoyl chloride (from palmitic acid, m. p. 63°), nitrobenzene, and aluminium chloride. The fraction of the product boiling at 235—240°/0·1 mm., after two crystallisations from acetone, melted at 44° (Fernholtz, Ansbacher, and MacPhillamy, *J. Amer. Chem. Soc.*, 1940, **62**, 430, give m. p. 44—45°). The 2 : 4-*dinitrophenylhydrazone*, red plates from alcohol, melted at 95—96° (Found: N, 10·1. $C_{32}H_{46}O_4N_4$ requires N, 10·2%).

By the Huang-Minlon reduction (4 hours at 160° and 20 hours at 230°) the crude hydrocarbon, b. p. 203°/0·5 mm., was obtained. It was dehydrogenated with palladium–charcoal (2 hours at 280°) and the product distilled at 200°/1 mm. Crystallisation from acetone yielded plates, m. p. 49·5° (Found: C, 88·5; H, 11·4. Calc. for $C_{26}H_{40}$: C, 88·6; H, 11·4%). Fernholtz, Ansbacher, and MacPhillamy (*loc. cit.*) give m. p. 45—46°; Kölbel and Fritsch (*loc. cit.*) give m. p. 35°.

(*b*) [By R. J. Rallings]. **2-*Naphthyl* n-*pentadecyl ketone*.** Pure palmitic acid, f. p. 62·6° (Smith, *J.*, 1931, 803), was converted into the acid chloride which was not distilled (it melted at 12°). With naphthalene and aluminium chloride in nitrobenzene the acid chloride gave the crude ketone, m. p. 56—59° (70%). Distillation at 240—245°/0·05 mm., followed by crystallisation from alcohol and then acetone, gave the pure ketone, m. p. 62—62·5° (Found: C, 85·1; H, 10·5. Calc. for $C_{26}H_{38}O$: C, 85·2; H, 10·4%). Buu-Hoï and Cagniant (*loc. cit.*) give m. p. 56°. The semicarbazone melted at 105° (Buu-Hoï and Cagniant, *loc. cit.*, give m. p. 97°) (Found: N, 9·7. Calc. for $C_{27}H_{41}ON_3$: N, 9·9%), and the 2 : 4-*dinitrophenylhydrazone*, red needles from alcohol or ethyl acetate, at 117—118° (Found: N, 10·0. $C_{32}H_{42}O_4N_4$ requires N, 10·2%). Hydrolysis of the semicarbazone gave back the ketone, m. p. 62—62·5°, and oxidation of the ketone with selenium dioxide followed by hydrogen peroxide (Morrell, Pickering, and Smith, *loc. cit.*) gave 2-naphthoic acid, m. p. and mixed m. p. 184°.

The pure semicarbazone, heated with sodium ethoxide in ethanol for 20 hours at 220°, gave the hydrocarbon, b. p. 200—210°/0·05 mm., m. p. 45—46° (85%). Crystallised from acetone it reached the constant m. p. 49·5°, as in the preparation (*a*) (Found: C, 88·8; H, 11·4%).

Infra-red Spectra.—These were recorded by Mrs. M. Broomfield, Physical Chemistry Group,

1-*Alkylnaphthalenes.*

Dodecyl		Tridecyl		Tetradecyl		Pentadecyl		Hexadecyl	
λ	log ε	λ	log. ε	λ	log ε	λ	log ε	λ	log ε
2618	3·63	2621	3·71	2617	3·57	2621	3·60	2618	2·97
2717	3·82	2715	3·94	2717	3·84	2718	3·83	2715	3·24
2783	3·81	2790	3·94	—	—	2785	3·84	—	—
2828	3·91	2831	4·03	2825	3·92	2826	3·93	2829	3·33
2891	3·73	2891	3·84	2885	3·72	2890	3·72	2893	3·14
2941	3·73	2941	3·84	2941	3·74	2940	3·73	2942	3·14
3037	2·96	3033	2·86	3038	2·99	3041	2·94	3040	2·91
3078	2·67	3078	2·58	3079	2·60	3071	2·68	3077	2·63
3098	2·60	3100	2·53	3108	2·55	3095	2·58	3102	2·59
3146	2·65	3141	2·58	3147	2·59	3142	2·65	3142	2·63
3182	2·13	3182	2·07	3185	2·10	3188	1·55	3186	1·15
3238	1·57	3248	1·57	3235	1·50	—	—	3239	0·54

2-*Alkylnaphthalenes.*

Dodecyl		Tridecyl		Tetradecyl		Pentadecyl		Hexadecyl	
λ	log ε	λ	log ε	λ	log ε	λ	log ε	λ	log ε
2561	3·52	2554	3·58	2559	3·76	2561	3·57	2561	3·62
2657	3·64	2654	2·72	2655	3·92	2654	3·70	2653	3·76
2757	3·70	2761	3·76	2758	3·96	2756	3·73	2765	3·81
2865	3·53	2868	3·60	2868	3·81	2868	3·56	2868	3·65
2972	2·66	—	—	—	—	2975	2·79	2980	2·77
3050	2·68	3059	2·58	3051	2·77	3048	2·79	3049	2·74
3094	2·38	3094	2·43	3092	2·51	3098	2·48	3094	2·45
3116	2·41	3117	2·47	3117	2·40	3117	2·52	3117	2·48
3146	2·25	3146	2·30	3146	2·39	3146	2·35	3146	2·39
3192	2·66	3193	2·66	3195	2·77	3195	2·79	3196	2·74
3248	1·61	3239	0·57	3252	1·67	3245	1·86	3242	1·72

Imperial Chemical Industries Limited, Billingham Division, on a Hilger D 209 Spectrometer (used on a single beam) with a prism of rock-salt. The comments by Anderson and Smith (*J. Inst. Petrol.*, 1952, **38**, 145) on the spectra of the lower naphthylalkanes apply here also. The two types of substitution (α- or β-) in the naphthalene nucleus can readily be distinguished.

Ultra-violet Spectra.—These were measured in *iso*octane solution by Mrs. M. Mikiewicz, Physical Chemistry Group, Imperial Chemical Industries Limited, Billingham Division, and are very similar to the spectra of the lower naphthylalkanes (see Anderson *et al.*, *loc. cit.*).

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90. *The Heats of Hydrolysis of Some Halides and Oxyhalides of Phosphorus.*

By T. CHARNLEY and H. A. SKINNER.

The heats of hydrolysis (at 25°) of liquid PCl_3, PBr_3, $POCl_3$, and crystalline $POBr_3$ have been measured, from which the respective heats of formation ($\Delta Hf°$) are derived as follows: −79·4, −46·5, −143·8, and −110·1 kcal./mole. Values of the *mean* bond dissociation energies, $\bar{D}$(P–Cl) = 77·9 and $\bar{D}$(P–Br) = 63·4 kcal./mole in PCl_3 and PBr_3 are calculated, and the P–O bond dissociation energies in the oxyhalides are: $D(O{=}PCl_3)$ = 121·8 and $D(O{=}PBr_3)$ = 119·3 kcal./mole.

NEALE and WILLIAMS (*J.*, 1952, 4535) have recently measured the heats of hydrolysis of phosphorus trichloride and oxychloride, obtaining significantly larger values than those due to Thomsen ("Thermochemische Untersuchungen," 1882, Vol. 2) and to Berthelot and Louguinine (*Ann. Chim. Phys.*, 1875, **6**, 305). The present studies were undertaken partly as an independent check on Neale and Williams's results, and more generally as a revision of the older thermal data on the halides and oxyhalides of phosphorus.

EXPERIMENTAL

(a) *Preparation of Compounds.*—Commercial samples of phosphorus trichloride, tribromide, and oxychloride were fractionated in nitrogen, and finally distilled into thin-glass ampoules in an all-glass, greaseless, vacuum system. Commercial phosphorus oxybromide was recrystallised from anhydrous ether, and purified by sublimation in a high vacuum.

(b) *The Calorimeter.*—This was a 1-l. narrow-necked Dewar vessel, as described by Charnley, Skinner, and Smith (*J.*, 1952, 2288). The experiments were carried out by breaking the ampoules under the surface of 750 g. of distilled water contained in the Dewar vessel, and following the resultant temperature changes in terms of the change in resistance of a shielded thermistor element immersed in the solution. Calibration of the calorimeter was done electrically, by the substitution method.

These hydrolyses proceed at a moderate speed only, requiring in some cases upwards of 30 min. to reach completion. Time–temperature curves with fore- and after-rating periods of at least 60 min. were taken in making due allowance for heat losses during the experiments.

All results are given in terms of the thermochemical calorie, 1 cal. = 4·1840 abs. joule. Experiments were carried out at 25°. The observed heats—quoted under $\Delta H_{obs.}$ in the tables of results—refer, in the case of the trihalide hydrolyses, to the reactions

$$PX_3\,(liq.) + (n + 3)H_2O\,(liq.) \longrightarrow [H_3PO_3 + 3HX]\text{ in }nH_2O\,(liq.) \quad . \; . \; . \quad (1)$$

and in the case of the oxyhalides to the reactions

$$POCl_3\,(liq.) + (n + 3)H_2O\,(liq.) \longrightarrow [H_3PO_4 + 3HCl]\text{ in }nH_2O\,(liq.) \quad . \; . \; . \quad (2)$$

and

$$POBr_3\,(cryst.) + (n + 3)H_2O\,(liq.) \longrightarrow [H_3PO_4 + 3HBr]\text{ in }nH_2O\,(liq.) \quad . \; . \quad (3)$$

The derived heats of formation, $\Delta Hf°$, make use of subsidiary thermochemical data on the heats of formation of water and of aqueous solutions of hydrogen chloride and bromide and of phosphorous and phosphoric acid. These assumed data were taken from the " Selected Values of Chemical Thermodynamic Properties," compiled by the National Bureau of Standards, Washington (Circular 500).

Results.—The results obtained are summarised in Table 1. We add the following comments : (*a*) PCl_3 : The mean value, $\Delta H_{obs.} = -67{\cdot}7 \pm 0{\cdot}5$ kcal./mole is in close agreement with the vale ($\Delta H = -67{\cdot}5$ kcal./mole) obtained by Neale and Williams (*loc. cit.*). Thomsen's earlier value (*loc. cit.*) was $\Delta H = -65{\cdot}1$ kcal/mole. (*b*) PBr_3 : Berthelot and Louguinine (*loc. cit.*) gave $\Delta H = -64{\cdot}0$ kcal./mole, compared with our mean value $\Delta H_{obs} = -67{\cdot}2 \pm 0{\cdot}6$ kcal./mole. (*c*) $POCl_3$: Thomsen found $\Delta H = -72{\cdot}2$ and Berthelot $-74{\cdot}6$ kcal./mole. Neale and Williams's value ($\Delta H = -79{\cdot}9$) is in much better agreement with the present mean, *viz.*, $\Delta H_{obs.} = -80{\cdot}4 \pm 0{\cdot}4$ kcal./mole. (*d*) $POBr_3$: Ogier (*Compt. rend.*, 1881, **92**, 83) reported $\Delta H = 79{\cdot}7$ kcal./mole for the heat of hydrolysis of crystalline $POBr_3$. The present mean value is $\Delta H_{obs.} = -80{\cdot}8 \pm 0{\cdot}5$ kcal./mole.

The older measurements of these hydrolysis heats were made at lower temperatures and in more concentrated solutions than the measurements now reported. Part of the discrepancy between the old and the new results is due to these causes.

TABLE 1.

Expt.	Wt. (g.)	*n* (moles)	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ (kcal.)	Expt.	Wt. (g.)	*n* (moles)	$\Delta H_{obs.}$ (kcal.)	$\Delta Hf°$ (kcal.)
	Reactant : PCl_3 (liq.).					Reactant : $POCl_3$ (liq.).			
1	0·7160	7,990	−67·0	−80·1	1	2·3484	2,720	−80·5	−143·6
2	1·1172	5,120	−68·0	−79·0	2	1·5674	4,070	−80·5	−143·6
3	0·7735	7,400	−67·3	−79·8	3	1·2213	5,230	−80·8	−143·4
4	1·3470	4,250	−67·8	−79·2	4	2·0604	3,100	−80·2	−143·9
5	0·6328	9,040	−68·1	−79·0	5	2·1465	2,970	−80·2	−143·9
6	0·6950	8,230	−68·0	−79·1	6	2·4066	2,650	−80·3	−143·8
	Mean values :		−67·7	−79·4		Mean values :		−80·4	−143·8
	Reactant : PBr_3 (liq.).					Reactant : $POBr_3$ (cryst.).			
1	2·7676	4,070	−66·8	−46·85	1	1·7698	6,740	−80·7	−110·2
2	1·2966	8,700	−67·3	−46·45	2	1·7512	6,815	−80·9	−110·0
3	2·6468	4,240	−67·8	−45·9	3	0·9634	12,390	−81·2	−109·8
4	2·1972	5,130	−66·6	−47·1	4	3·3728	3,540	−80·6	−110·1
5	0·9303	12,095	−67·6	−46·2	5	1·5552	7,670	−80·7	−110·2
	Mean values :		−67·2	−46·5		Mean values :		−80·8	−110·1

DISCUSSION

The values of $\Delta Hf°$ given in Table 1 refer to the *liquid* state in case of phosphorus trichloride, tribromide, and oxychloride, and to the *crystalline* state of phosphorus oxybromide. The errors in these $\Delta Hf°$ include the experimental errors in $\Delta H_{obs.}$, and errors present in the assumed thermal data. Of these, the errors in $\Delta Hf°$ (H_2O, liq.) and $\Delta Hf°$(HCl, aq.) are small ($\pm 0{\cdot}010$ and $\pm 0{\cdot}040$ kcal./mole, respectively). The errors in $\Delta Hf°(H_3PO_3$, aq.) and $\Delta Hf°(H_3PO_4$, aq.) may, however, be more significant. The National Bureau of Standards recommended value, $\Delta Hf°(H_3PO_4$, cryst.) $= -306{\cdot}2$ kcal./mole, is derived from a series of experiments by Thomsen (*loc. cit.*), the overall accuracy of which is difficult to assess; some independent measurements by Giran (*Ann. Chim. Phys.*, 1903, **30**, 203) confirm Thomsen's value, so that in this case one might accept the chosen value with some degree of confidence. The value $\Delta Hf°$ (H_3PO_3, cryst.) $= -232{\cdot}2$ kcal./mole is also derived from a series of data due to Thomsen, but in this case confirmatory evidence is lacking and the accuracy of the value is a matter for speculation. The *overall* error limits in $\Delta Hf°$ values now reported cannot therefore be given in a strict manner : in the case of the oxyhalides [involving $\Delta Hf°$ (H_3PO_4)], they should not exceed ± 1 kcal./mole. The conversion of the $\Delta Hf°$ of Table 1 into gaseous-state values in Table 2 makes use of the heats of vaporisation ($\lambda_{vap.}^{25}$) given in the N.B.S. Circular 500. The heat of sublimation of solid phosphorus oxybromide is an estimate.*

* The N.B.S. tables give $\lambda_{vap.}^{192} = 9{\cdot}1$ kcal./mole. The corresponding value at 25°, we estimate at 11·5—12 kcal. To this is added an estimated heat of fusion of 3—4 kcal., leading to $\lambda_{sub.} = 15 \pm 1$ kcal.

Values given under $\bar{D}$(P–X) in Table 2 are the calculated *mean* bond dissociation energies* of P–X bonds in PX_3. In the final column, the values given are of the $O{=}PX_3$ bond dissociation energies. The $\bar{D}$ values differ from those given by Pauling ("Nature of the Chemical Bond," p. 53, 1940, Cornell Univ. Press), partly through the changes in $\Delta Hf°(PX_3)$,

TABLE 2.

Molecule	$\Delta Hf°$	λ^{25}	$\Delta Hf°$ (g.)	$\bar{D}$(P–X)	$D(O{=}PY_3)$
PCl_3 (liq.)	− 79·4	7·8	− 71·6	77·9	—
PBr_3 (liq.)	− 46·5	11·6	− 34·9	63·4	—
$POCl_3$ (liq.)	−143·8	9·5	−134·3	—	121·8
$POBr_3$ (cryst.)	−110·1	15	− 95·1	—	119·3
POF_3	—	—	—	—	129·8

but mainly by the adoption of the value for $\Delta Hf°$ (P, g.) given in the N.B.S. tables (75·18 kcals.). The value given for $D(O{=}PF_3)$ is derived from Ebel and Bretscher's data (*Helv. Chim. Acta*, 1929, **12**, 450), who measured the heat of oxidation of PF_3 directly.

The structure of POX_3 may be formulated either as $O{=}PX_3$, or as $O{\leftarrow}PX_3$: both structures may represent extremes from which a resonance hybrid is constructed, but it is of interest to consider which structure is the dominating one. Phillips, Hunter, and Sutton (*J.*, 1945, 146) have discussed this point, concluding from the evidence of dipole moments and bond-lengths, that the O–P bonds in POX_3 resemble double, rather than single bonds. The bond-energy data point in the same direction.

A reliable evaluation of the energy of the single-bonded P–O link cannot yet be made. Recently, Koerner and Daniels (*J. Chem. Physics*, 1952, **20**, 113) reported a measurement of the heat of formation of liquid P_4O_6, from which we have derived $\Delta Hf°(P_4O_6, g.) = -530$ kcal./mole, and $\bar{D}$(P–O) = 98·8 kcal./mole. Their value was obtained by an indirect experimental method, and for this reason requires confirmation. The P–O bond strength range of 120—130 kcal./mole in POX_3 lies well above the single-bonded $\bar{D}$(P–O) value, and is consistent with a considerable degree of double-bonded character in the $O{-}PX_3$ linkages.

The decrease in $D(O{=}PX_3)$ as X changes through $F \longrightarrow Cl \longrightarrow Br$ follows the order that might be expected if steric repulsion forces between the X_3 grouping and the O atom were appreciable. Williams, Sheridan, and Gordy (*J. Chem. Physics*, 1952, **20**, 164) found, however, the same bond-length for P–O (1·45 Å) in POF_3 as in $POCl_3$, and the simple steric explanation of the variations in $D(O{=}PX_3)$ seems inadequate.

The authors thank Mr. E. Neale and Mr. L. T. D. Williams, of Porton, who drew their attention to the problem, and Mr. N. B. Smith for some considerable assistance in the calorimetric studies on phosphorus tribromide.

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* $\bar{D}$(P–X) is one-third of the heat of atomization of PX_3 (gas) into normal gaseous atoms. The $\Delta Hf°$ of the atoms are from the N.B.S. tables.

91. *The Dehydration and Racemisation of* N-*Acyl*-L-*aspartic Acids by Acetic Anhydride.*

By C. C. Barker.

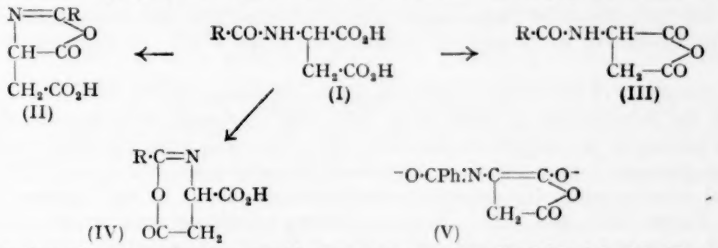
The salts of *N*-acetyl- and *N*-benzoyl-L-aspartic acids resist racemisation by aqueous acetic anhydride and evidence is adduced to show that they form internal anhydrides rather than oxazolones under these conditions.

Two crystalline products formed from *N*-acetyl-L-aspartic acid by acetic anhydride have been identified as the racemic and the optically active form of *N*-acetylaspartic anhydride, and not, as has been claimed by earlier workers, 2-methyl-5-oxazolon-4-ylacetic acid and *N*-acetyl-L-aspartic anhydride, respectively. The anhydride structure usually attributed to the dehydration product from *N*-benzoyl-L-aspartic acid has been confirmed.

The behaviour of *N*-acetyl- and *N*-benzoyl-L-aspartic anhydride with aqueous sodium hydroxide is described and discussed.

Optically active α-acetamido-acids are readily racemised by treating aqueous solutions of their salts with acetic anhydride (du Vigneaud and Meyer, *J. Biol. Chem.*, 1932, **98**, 295). This process, which is general, has been successfully applied by Barker, Hughes, and Young (*J.*, 1952, 1574) to a benzoylated hydrolysate obtained from gliadin in order to estimate the total glutamic acids (D plus L) by the method of isotope dilution. An attempt to apply the same process to the estimation of total aspartic acids revealed that neither *N*-acetyl- nor *N*-benzoyl-L-aspartic acid was readily racemised and thus led to the present investigation.

Because an *N*-acylaspartic acid (I) is both an α- and a β-acylamino-acid, it presents the possibility of dehydration to an oxazolone (II), a true anhydride (III), or a 5 : 6-dihydro-6-keto-1 : 3-oxazine (IV). Since the intermediate formation of (II) is the essential step in



the racemisation of an α-acylamino-acid by aqueous acetic anhydride (cf. *Adv. Protein Chem.*, 1948, **4**, 356), the preferential formation of (III) or (IV) would account for its failure in this case. The only recorded instance of the dehydration of a β-acylamino-acid to a 1 : 3-oxazine derivative is the conversion of β-benzamido*iso*valeric acid into 5 : 6-dihydro-6-keto-4 : 4-dimethyl-2-phenyl-1 : 3-oxazine by Baker and Ollis (*J.*, 1949, 345), who point out that this type of compound could play a part in the chemistry of aspartic acid. Some further observations on the dehydration of β-benzamido-carboxylic acids will be offered in a later paper.

The dehydration of *N*-acetyl-L-aspartic acid by acetic anhydride has been examined by Harington and Overhoff (*Biochem. J.*, 1933, **27**, 338), who reported the isolation of an oxazolone (II; R = Me), m. p. 145—146°, when the dry acid was boiled with acetic anhydride, and of a true anhydride (III; R = Me), m. p. 175°, from the moist acid and acetic anhydride at 95°. They obtained *N*-acetyl-L-aspartic acid as a microcrystalline solid, m. p. 142—143°, by acetylation of an aqueous, alkaline solution of L-aspartic acid with acetic anhydride, but in the present work this procedure invariably gave a syrup which contained traces of sodium acetate. Gordon, Martin, and Synge (*Biochem. J.*, 1943, **37**, 82) also record this acid as a syrup. Dehydration of this acetate-containing material gave an optically inactive compound, m. p. 143—144°, identical with that prepared by dehydrating crystalline, acetate-free *N*-acetyl-DL-aspartic acid. Dehydration of acetate-

free *N*-acetyl-L-aspartic acid, however, gave a material, m. p. 173°, which was hydrolysed by hydrochloric acid to give L-aspartic acid free from the D-isomer. The two dehydration products gave a mixed m. p. 156—160° and are clearly racemic and optically active forms of the same compound. The acetate-free *N*-acetyl-L-aspartic acid was produced as a syrup by acetylating an aqueous solution of L-aspartic acid without the addition of alkali. It was subsequently found possible to obtain it crystalline (m. p. 140—141°) by evaporating an aqueous solution of the optically active dehydration product. The crystalline acid induced crystallisation of the crude, non-crystalline acid produced by acetylation of L-aspartic acid, but recrystallisation of this acid was not a practicable means of purification.

The dehydration product, m. p. 143—144°, was given the oxazolone structure by Harington and Overhoff (*loc. cit.*) because it gave 2-methyl-5-oxazolon-4-ylacetyl chloride when treated with phosphorus pentachloride. Such behaviour, however, is not incompatible with the anhydride structure (II; R = Me) and this structure is now attributed to both the dehydration products for following reasons: (i) Both substances failed to react with diazomethane, implying the absence of carboxyl groups. (ii) Both substances reacted with ammonia to give amides, yielding acetaldehyde when treated with sodium hypobromite and then hydrolysed with 20% sulphuric acid. The acetaldehyde could only have arisen by decarboxylation of formylacetic acid produced by degradation of *N*-acetylaspartic α-amide. The 1 : 3-oxazine derivative (IV) could not give rise to an α-amide. (iii) The racemic dehydration product, m. p. 143—144°, gave with aniline a mixture of anilides from which the less soluble *N*-acetyl-DL-aspartic β-anilide, m. p. 198—199°, was readily isolated. The structure of this follows from its dehydration to a crystalline oxazolone, which gave with ammonia *N*-acetyl-DL-aspartic α-amide β-anilide. The latter was identified as an α-amide by the reaction previously used to identify *N*-acetylaspartic α-amide. The formation of mixed anilides is only compatible with the anhydride structure (III). (iv) The complete absence of racemisation when the optically active dehydration product was hydrolysed by hydrochloric acid is incompatible with the oxazolone structure (II) ("The Chemistry of Penicillin," Princetown Univ. Press, Princetown, New Jersey, p. 742).

A similar study of the action of diazomethane, ammonia, and hydrochloric acid, respectively, on the dehydration product, m. p. 204—205°, obtained from *N*-benzoyl-L-aspartic acid, has confirmed the anhydride structure (III; R = Ph) generally attributed to it.

It was previously reported that unpurified *N*-acetyl-L-aspartic acid retained 87% of its optical activity under the racemising conditions employed by du Vigneaud and Meyer (Barker, *Nature*, 1951, **168**, 908). It has now been found that an aqueous solution of the pure acid, prepared by dissolving recrystallised *N*-acetyl-L-aspartic anhydride in water, retained 96% of its optical activity when treated in the same manner. When the same racemising process was applied to *N*-benzoyl-L-aspartic acid only 76% of its optical activity was retained; when L-asparagine was benzoylated in aqueous sodium hydrogen carbonate and the resulting solution treated with acetic anhydride, the product retained only 5% of its optical activity. The last result is attributed to the ability of *N*-benzoyl-L-asparagine to form an oxazolone but not an anhydride.

Much more extensive racemisation occurred when pre-formed *N*-acylaspartic anhydrides were treated with aqueous alkali. *N*-Acetyl-L-aspartic anhydride retained 35% of its optical activity with N-sodium hydroxide at room temperature, while *N*-benzoyl-L-aspartic anhydride was completely racemised at the same temperature. The latter anhydride was insoluble in water but in N-sodium hydroxide immediately gave a faintly yellow solution which showed a strong, blue fluorescence under ultra-violet light. Both the colour and fluorescence faded as hydrolysis of the anhydride proceeded. The solubility, fluorescence, and racemisation can be explained by postulating the formation of the ion (V) in which the benzene ring is conjugated with two enolic double bonds. The absence of this stabilising conjugation in the corresponding ion derived from *N*-acetyl-L-aspartic anhydride can well explain its reduced tendency to racemise.

The isolation of crystalline anhydrides from these *N*-acylaspartic acids and acetic anhydride does not, of course, preclude the presence of other dehydration products in

equilibrium in solution. The partial racemisation produced by du Vigneaud and Meyer's method may take place through intermediate formation of small amounts of oxazolone, but it is pertinent that *N*-benzoyl-L-aspartic acid forms considerable amounts of the anhydride under these conditions as judged by the formation of a strong, blue fluorescence on addition of sodium hydroxide.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

N-*Acetyl*-L-*aspartic Acid*.—Acetic anhydride (25 c.c.) was added to a solution of L-aspartic acid (5 g.) in hot water (100 c.c.), the mixture cooled quickly to room temperature, more acetic anhydride (75 c.c.) added, and the whole stirred for 6 hours at 20° (cooling). A sample of the reaction product then gave no colour when buffered with sodium hydrogen carbonate and heated with ninhydrin. Removal of the solvents at 11 mm. gave *N*-acetyl-L-aspartic acid as a gum (6·7 g.), which, since it was free from metal acetates, could be used without purification in the preparation of *N*-acetyl-L-aspartic anhydride. This gum slowly crystallised when seeded and, after being washed with a little aqueous acetone and dried (P_2O_5), yielded microcrystalline *N*-acetyl-L-aspartic acid, m. p. 139—140°. Harington and Overhoff (*loc. cit.*) give m. p. 142—143°.

N-*Acetyl*-L-*aspartic Anhydride*.—Acetic anhydride (30 c.c.) and non-crystalline, acetate-free *N*-acetyl-L-aspartic acid (5 g.) were heated at 95—100° for 20 minutes. The resulting solution was filtered, reduced to half-volume at 11 mm., and cooled in ice for an hour. The crystalline *N*-acetyl-L-aspartic anhydride (2·7 g.) was washed with acetic anhydride, ethyl acetate, and finally light petroleum (b. p. 40—60°) and had m. p. 170—173°. Recrystallisation from acetic anhydride raised the m. p. to 173° [Harington and Overhoff (*loc. cit.*) give m. p. 175°] (Found: N, 8·8. Calc. for $C_6H_7NO_4$: N, 8·9%). Evaporation of an aqueous solution of the anhydride gave *N*-acetyl-L-aspartic acid as a syrup which slowly crystallised (m. p. 140—141°).

N-*Acetyl*-DL-*aspartic Anhydride*.—(*a*) *N*-Acetyl-DL-aspartic acid (5 g.) was prepared and dehydrated in the same manner as the optically active acid, giving *N*-acetyl-DL-aspartic anhydride (2·2 g.), m. p. 143—144° (Found: N, 8·7%). Harington and Overhoff (*loc. cit.*) describe this substance as 2-methyl-5-oxazolon-4-ylacetic acid and give m. p. 145—146°.

(*b*) *N*-Acetyl-L-aspartic acid, obtained as a syrup containing a little sodium acetate by aqueous alkaline acetylation of L-aspartic acid (Harington and Overhoff, *loc. cit.*), was dehydrated as in (*a*). The yield of *N*-acetyl-DL-aspartic anhydride, m. p. 143—144°, was similar.

N-*Acetyl*-DL-*aspartic* β-*Anilide*.—*N*-Acetyl-DL-aspartic anhydride (3·7 g.) was added to a solution of aniline (5 g.) in absolute ethyl alcohol (15 c.c.). The mixture became warm and gave a clear solution which quickly deposited crystals. Next morning the mixture was acidified with N-hydrochloric acid, the precipitate dissolved in dilute sodium hydroxide solution, the whole extracted with ether to remove aniline, and the aqueous layer acidified. After being kept at 0° overnight the precipitate was filtered off and washed with water. This crude material (4·3 g.), m. p. 180—182° (frothing), was boiled with 95% ethyl alcohol (40 c.c.), the mixture allowed to cool to room temperature, and the process repeated, giving *N-acetyl*-DL-*aspartic* β-*anilide* (2·9 g.), m. p. 197—198°. Recrystallisation from 95% ethyl alcohol raised the m. p. to 198—199° (Found: C, 57·3; H, 5·8; N, 11·4. $C_{12}H_{14}O_4N_2$ requires C, 57·6; H, 5·6; N, 11·2%). By evaporation of the combined alcoholic filtrates there was obtained a mixture, m. p. 176—179° (frothing), of *N*-acetyl-DL-aspartic α- and β-anilide (Found: C, 57·5; H, 5·8; N, 11·3%; equiv., 250. Calc. for $C_{12}H_{14}O_4N_2$: equiv., 250·3).

2-*Methyl*-5-*oxazolon*-4-*ylacetanilide*.—*N*-Acetyl-DL-aspartic β-anilide (1·0 g.) and acetic anhydride (5 c.c.) were heated at 95° for 20 minutes, the solvent removed at 11 mm., and the resulting syrup induced to crystallise by addition of a little ethyl acetate. The crystals were washed with benzene–ethyl acetate and then with light petroleum (b. p. 40—60°), giving 2-*methyl*-5-*oxazolon*-4-*ylacetanilide* (0·9 g.), m. p. 160° (from absolute ethyl alcohol) (Found: C, 61·6; H, 5·2; N, 11·7. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

N-*Acetyl*-DL-*aspartic* α-*Amide* β-*Anilide*.—2-Methyl-5-oxazolon-4-ylacetanilide (0·45 g.) was kept with aqueous ammonia (2 c.c.; *d* 0·88) for 12 hours and the resulting solid washed with water and dried. Recrystallisation from ethyl alcohol (63 c.c.) gave the α-*amide* β-*anilide* (0·38 g.), m. p. 216—218° (Found: C, 57·5; H, 6·0; N, 16·8. $C_{12}H_{15}O_3N_3$ requires C, 57·8; H, 6·1; N, 16·9%).

Ice-cold, 0·25N-sodium hypobromite was prepared by adding bromine (0·3 c.c.) to sodium hydroxide (1·4 g.) in water (12 c.c.) at 0°. *N*-Acetyl-DL-aspartic α-amide β-anilide (0·30 g.) was

added to 3·0 c.c. of this solution and stirred at 0° for 5 minutes and then at room temperature for 5 minutes, at the end of which the amide had dissolved. The solution was then kept at 50° for 5 minutes, sodium metabisulphite added until a negative reaction was obtained with starch–iodide paper, aqueous sulphuric acid (10 c.c.; 20%) added, and the solution slowly distilled into aqueous *p*-nitrophenylhydrazine hydrochloride. Acetaldehyde *p*-nitrophenylhydrazone (0·050 g.) was precipitated and, after crystallisation, had m. p. 129° alone and admixed with authentic material.

Degradation of N-*Acetyl- and* N-*Benzoyl-aspartic Amide.*—(*a*) *N*-Acetyl-DL-aspartic anhydride (0·70 g.) was added to aqueous ammonia (4 c.c.; *d* 0·88) and, after 30 minutes, the solution evaporated to dryness at 11 mm. Ice-cold, aqueous sodium hypobomite containing sodium hydroxide (2·0 g.) and bromine (0·62 c.c.) was added and the mixture worked up as in the previous degradation. Acetaldehyde *p*-nitrophenylhydrazone (0·29 g.) was obtained (m. p. and mixed m. p. 129°). Degradation of *N*-acetyl-L-aspartic anhydride gave similar results.

(*b*) *N*-Benzoyl-L-aspartic anhydride (1·0 g.) was added to aqueous ammonia (4 c.c.; *d* 0·88); after 2 hours the solution was diluted and acidified, and the precipitated amide(s) added to ice-cold, aqueous sodium hypobromite (11·5 c.c.; prepared as described for the α-amide β-anilide) and worked up as above. Acetaldehyde *p*-nitrophenylhydrazone (0·20 g.) was obtained (m. p. and mixed m. p. 129°).

N-*Benzoyl*-L-*aspartic Anhydride.*—*N*-Benzoyl-L-aspartic acid (5 g.; Fischer, *Ber.*, 1899, **32**, 2459) and acetic anhydride (25 c.c.) were heated at 100° for 30 minutes, reduced to 5 c.c. at 11 mm., and cooled in ice. The crystalline solid (3·5 g.) was recrystallised from a minimum of acetic anhydride and washed with dry acetone; it had m. p. 204—205° (Found: N, 6·2. Calc. for $C_{11}H_9O_4N$: N, 6·4%). Pauly and Weir (*Ber.*, 1910, **43**, 665) prepared this substance using acetyl chloride as dehydrating agent and gave m. p. 208—209° (corr.).

Racemisation of N-*Acetyl- and* N-*Benzoyl*-L-*aspartic Acid.*—(Specific rotations are calculated on the aspartic acid content.) (*a*) *N*-Acetyl-L-aspartic anhydride (1·238 g.), dissolved in water (5 c.c.), was kept overnight to ensure complete hydrolysis to *N*-acetyl-L-aspartic acid. The temperature was raised to 40°, hydrated sodium acetate (1 g.) and acetic anhydride (15 c.c.) were added, and the stirred mixture was kept at 40° for 8 hours. The resulting solution was evaporated to dryness over soda–lime in a vacuum desiccator, 6N-hydrochloric acid (15 c.c.) added, and the solution kept at 95° for 4 hours and then made up to 25 c.c. with 6N-hydrochloric acid. It then had $[\alpha]_D^{20}$ +23·8° (based on aspartic acid; $l = 2$) (duplicate, +23·2°). The two results correspond to an average racemisation of 4%. A control hydrolysis of *N*-acetyl-L-aspartic anhydride (0·7324 g. in 25 c.c. of 6N-hydrochloric acid) gave $[\alpha]_D^{20}$ +24·4° ($l = 2$).

(*b*) *N*-Benzoyl-L-aspartic acid (0·7608 g.) was treated as above, but the hydrolysate was extracted with benzene to remove benzoic acid and made up to 10 c.c. It gave $[\alpha]_D^{20}$ +18·5° (based on aspartic acid; $l = 1$), which corresponds to 24·5% racemisation. A control hydrolysis of *N*-benzoyl-L-aspartic acid (1·018 g.) gave $[\alpha]_D^{20}$ +24·5° (25 c.c.; $l = 2$).

Racemisation of N-*Acetyl- and* N-*Benzoyl*-L-*aspartic Anhydride.*—(*a*) *N*-Acetyl-L-aspartic anhydride (0·4652 g.) was kept in N-sodium hydroxide (8 c.c.) for 8 hours. Concentrated hydrochloric acid (11 c.c.) was added, and the whole kept at 95° for 4 hours, cooled to 20°, and made up to 25 c.c. with 6N-hydrochloric acid. It then gave $[\alpha]_D^{20}$ +8·6° (based on aspartic acid; $l = 2$), which corresponds to 65% racemisation.

(*b*) *N*-Benzoyl-L-aspartic anhydride (0·6512 g.) was dissolved in N-sodium hydroxide at room temperature, to give a faintly yellow solution which showed a strong, blue fluorescence under ultra-violet light. The colour and fluorescence faded completely during 3 hours. The solution was worked up as above with the inclusion of a benzene extraction to remove benzoic acid. It gave $\alpha_D^{20} = 0{\cdot}00°$ ($l = 2$).

Racemisation of N-*Benzoyl*-L-*asparagine.*—L-Asparagine (1·40 g.; monohydrate) and sodium hydrogen carbonate (3·4 g.) were dissolved in water (15 c.c.), benzoyl chloride (2·3 c.c.) was added, and the whole stirred at 0—5° for 6 hours, whereafter acetic anhydride (15 c.c.) was added and stirring continued for a further 12 hours. Subsequent procedure followed that described for the racemisation of *N*-benzoyl-L-aspartic acid and gave $[\alpha]_D^{20}$ +1·1° (based on aspartic acid; 25 c.c., $l = 2$), which corresponds to 95·5% racemisation.

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92. *The Chemistry of the Triterpenes. Part XIII.* The Further Characterisation of Polyporenic Acid A.*

By R. G. Curtis, Sir Ian Heilbron, E. R. H. Jones, and Gilbert F. Woods.

Polyporenic acid A, a diethenoid dihydroxy-monocarboxylic sapogenin from the birch-tree fungus *Polyporus betulinus* Fr., has been further characterised. Both hydroxyl groups are secondary and exhibit different reactivities as do the corresponding ketones. On melting, polyporenic acid A decomposes smoothly and in good yield, to give a decarboxy-compound which has also been characterised. The significance of the molecular-rotation changes involved in the formation of these derivatives is discussed.

In 1939 Cross, Eliot, Heilbron, and Jones (*J.*, 1940, 632) commenced a systematic investigation of the constituents of the higher fungi with a re-investigation of the birch-tree fungus, *Polyporus betulinus* Fr., which resulted in the isolation of polyporenic acids A, B, and C. It was suggested that these acids might be triterpenoid in nature; acids A and B appeared to be isomeric $C_{30}H_{48}O_4$ compounds containing one carboxyl group, two hydroxyl groups, and two ethylenic double bonds. The work was extended by Cross and Jones (*J.*, 1940, 1491), with an investigation of the unsaturated system of polyporenic acid A. Of the two double bonds present only one could be hydrogenated catalytically at ordinary temperature and pressure, and it was concluded from ozonolysis experiments that the reactive double bond was present as a vinylidene group ($CH_2{=}C<$). Owing to the war the work had then to be abandoned with the consequence that the three acids were not characterised unequivocally.

Unknown to Cross *et al.* (*locc. cit.*) a chemical study of the constituents of *Polyporus betulinus* Fr. had been carried out just previously by Frèrejacque (*Reviews Myc.*, 1938, **3**, 95) who succeeded in isolating a new compound, m. p. 185—187° (decomp.), $[\alpha]_D$ +71·5° (in methanol), which he designated ungulinic acid. Subsequently, Locquin, Locquin, and Prevot (*ibid.*, 1948, **13**, 3) repeated the isolation of polyporenic acid A and confirmed its identity with ungulinic acid.

The present communication concerns the isolation and purification of substantial quantities of polyporenic acid A, and an investigation of the chemistry of the acid as a foundation for a more vigorous attack on the problem of its structure. Large quantities of *Polyporus betulinus* Fr. were supplied through the courtesy of Mr. G. D. Rouse of H.M. Forestry Commission (Lyndhurst). The method employed for extracting the acid was similar to that developed by Cross *et al.* (*loc. cit.*) with slight modifications because of the much larger quantities involved and the fact that the exclusive isolation of acid A was aimed at. The latter was entirely successful and only traces of the higher-melting acids were detected. Initially the spore tissue was separated from the fleshy part of the fungus and extracted separately. However, the yield of acid A was the same as from the bulk fungus and subsequently the tedious process of separation was abandoned.

The physical constants of the acid and its methyl ester agreed closely with those reported earlier, the melting point discrepancies being due to our use of a Kofler hot stage. The acid forms a series of salts with amines, but these, of which the *cyclo*hexylamine salt is typical, have characteristic, though poorly defined, melting properties and have not proved useful for the isolation or purification of the acid (cf. Harris and Sanderson, *J. Amer. Chem. Soc.*, 1948, **70**, 334).

The equivalent weight of polyporenic acid has been redetermined and as before corresponds to a formula of $C_{31}H_{50}O_4$. The analytical data, however, fit the formula $C_{30}H_{48}O_4$ rather better than $C_{31}H_{50}O_4$ (cf. following paper) and at the moment no clear decision can be made between these two formulæ. Because of the prevalence of C_{30} and the absence of C_{31} cyclic compounds in Nature the calculated analytical figures in the experimental section and the formulæ quoted in this and the two following papers are based on $C_{30}H_{48}O_4$ for polyporenic acid A, but this does not imply our acceptance of this formula over $C_{31}H_{50}O_4$.

* Part XII, *J.*, 1952, 2868.

The presence of two ethylenic linkages has been confirmed by perbenzoic acid titration of the triol formed by lithium aluminium hydride reduction of the methyl ester. Two hydroxyl groups, designated *a* and *b*, have been characterised in the methyl ester by formation of an *a*-acetate, an *a*-benzoate, and an *a* : *b*-diacetate. Attempts to prepare an *a* : *b*-dibenzoate were unsuccessful. Diacetylation was carried out at 20° by Whitman and Schwenk's method (*J. Amer. Chem. Soc.*, 1946, **68**, 1865), a trace of anhydrous perchloric acid being used as catalyst. Cross *et al.* (*loc. cit.*) described methyl polyporenate A monoacetate, m. p. 112°, $[\alpha]_D$ +88°, which we now consider must have been the *a* : *b*-diacetate, m. p. 118·5—120°, $[\alpha]_D$ +87°, thus explaining the unsuccessful attempts further to acetylate the supposed monoacetate. Further, the monoformate described by Cross and Jones (*loc. cit.*) was most likely the diformate.

That both hydroxyl groups are secondary has been established by chromic acid oxidation to the corresponding ketones. The method employed was adapted from that used for the oxidation of acetylenic carbinols (see Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39), and involved the addition of a standard aqueous sulphuric acid solution of chromium trioxide to an acetone solution of the compound at 20°. The reagent oxidises a primary hydroxyl group to a carboxyl group. Thus, the triol mentioned above was oxidised to *a* : *b*-diketopolyporenic acid A, identical with the compound produced by similar oxidation of acid A. As was expected the acid and its methyl ester formed diketones and the methyl ester *a*-acetate and *a*-benzoate formed monoketones, thus confirming the presence of a free hydroxyl group in the latter compounds.

The different reactivities of the hydroxyl groups in polyporenic acid A are reflected in the properties of the keto-groups which are formed on oxidation. The *a*-carbonyl group reacted readily with the usual carbonyl reagents whereas the *b*-carbonyl group failed to react even under vigorous conditions. The somewhat sterically hindered location of the *b*-hydroxyl group became evident when attempts to prepare the C_{29}-hydrocarbon by Wolff–Kishner reduction of the decarboxy- *a* : *b*-diketo-compound (see below) resulted in the isolation of two compounds both of which still contained oxygen. This behaviour is analogous to that of diketosumaresinolic acid (Ruzicka, Jeger, Grob, and Hosli, *Helv. Chim. Acta*, 1943, **26**, 2283), the unreactive carbonyl group of which failed to react with carbonyl reagents and resisted reduction under Wolff–Kishner and Clemmensen conditions. The presence of an unreactive carbonyl group has been established by infra-red examination. The infra-red absorption data are discussed in the following paper. *b*-Ketopolyporenic acid A and its methyl ester *a*-acetate also exhibited selective low intensity absorption at 2920—2930 Å ($\varepsilon = 450$) and 2900 Å ($\varepsilon = 270$) respectively. The molecular-extinction coefficients of these two bands are appreciably higher than would be expected for isolated carbonyl groups. This is almost certainly due in each case to the presence of a trace of a conjugated diene, the formation of which will be discussed in a later paper.

The absence of high-intensity absorption at 2200—2600 Å in any of the carbonyl derivatives of polyporenic acid A precludes the presence of αβ-unsaturation. Further, absence of ferric chloride coloration and characteristic α- or β-diketone absorption shows that the hydroxyl groups are separated from the double bonds by at least one saturated carbon atom and that the two hydroxyl groups are separated from each other by at least two carbon atoms. The absence of selective absorption in the parent acid precludes the conjugation of the double bonds either with each other or with the carboxyl group. Finally, the comparative stability of *a* : *b*-diketopolyporenic acid A shows that neither of the hydroxyl groups is β- to the carboxyl group.

When melted in a capillary, polyporenic acid A readily underwent decomposition with frothing and evolution of a volatile component (cf. morolic acid, Barton and Brooks, *J.* 1951, 257). The resultant clear melt solidified on cooling and remelted at a much lower temperature. A quantitative study of the reaction revealed that it involved simply the elimination of carbon dioxide without any concurrent dehydration. Melting the acid in an inert atmosphere gave the decarboxy-compound in good yield, and it was characterised as its *a*-acetate, *a*-benzoate, and *a* : *b*-diacetate. The relative reactivities of the hydroxyl groups and the corresponding carbonyl groups were the same as in the parent acid. Conjugation of the double bonds was again precluded by the absence of selective light absorption

above 2200 Å. The decarboxy-diketo-compound also failed to show any high-intensity absorption, proving the complete absence of any conjugation between the two carbonyl groups and the two double bonds.

The molecular-rotation differences (cf. Barton and Jones, *J.*, 1944, 659) of polyporenic acid A and its derivatives are shown in Tables 1—5. For the purpose of direct comparison the rotation of the acid was determined in chloroform, but for characterisation the more accurate value is that determined in pyridine, because of the comparative insolubility of the acid in chloroform. It will be seen that, in agreement with general experience, simple changes produce regular molecular-rotation differences in polyporenic acid A. The

TABLE 1. *Esterification of acids.*

Compound	$[M]_D$, acid	$[M]_D$, Me ester	Δ
Polyporenic acid A	+350°	+386°	+36°
b-Keto-acid A	+362	+370	+ 8
a : *b*-Diketo-acid A	+494	+507	+13

TABLE 2. *Acetylation.*

	$[M]_D$					
Compound	Diol	*a*-Ac	*a* : *b*-Diac	Δ(*a*)	Δ(*b*)	Δ(*a* : *b*)
Acid A methyl ester	+386°	+175°	+497°	−211°	+322°	+111°
Dihydro-(I)-acid A methyl ester	+374	+170	+458	−204	+288	+ 84
Dihydro-(II)-acid A methyl ester	+379	+207	+498	−172	+291	+119
Decarboxy-compound	+296	+104	+405	−192	+301	+109
b-Keto-acid A methyl ester	+370	+237	—	−133	—	—

Δ(*a*) = $[M]_D$, *a*-acetate − $[M]_D$, diol. Δ(*b*) = $[M]_D$, *a* : *b*-diacetate − $[M]_D$, *a*-acetate.
Δ(*a* : *b*) = $[M]_D$, *a* : *b*-diacetate − $[M]_D$, diol.

TABLE 3.—*Benzoylation of the* a*-hydroxyl group.*

Compound	$[M]_D$, Diol	$[M]_D$, *a*-Monobenzoate	Δ
Acid A methyl ester	+386°	+ 74°	−312°
b-Keto-acid A methyl ester	+370	+147	−223
Decarboxy-compound	+296	− 27	−323

TABLE 4. *Oxidation.*

	$[M]_D$					
Compound	Alcohol	*b*-Ketone	*a* : *b*-Dione	Δ(*b*)	Δ(*a*)	Δ(*a* : *b*)
Polyporenic acid A	+350°	+362°	+494°	+12°	+132°	+144°
Acid A methyl ester	+386	+370	+507	−16	+137	+121
Methyl ester *a*-acetate	+175	+237	—	+62	—	—
Methyl ester *a*-benzoate	+ 74	+147	—	+73	—	—
Decarboxy-compound	+296	—	+427	—	—	+131

Δ(*b*) = $[M]_D$, *b*-ketone − $[M]_D$, alcohol. Δ(*a*) = $[M]_D$, *a* : *b*-dione − $[M]_D$, *b*-ketone.
Δ(*a* : *b*) = $[M]_D$, *a* : *b*-dione − $[M]_D$, alcohol.

TABLE 5. *Decarboxylation.*

Compound	$[M]_D$, Acid or Me ester	$[M]_D$, Decarboxy-compound	Δ
Polyporenic acid A	+350°	+296°	− 54°
Acid A methyl ester	+386	+296	− 90
Methyl ester *a*-acetate	+175	+104	− 71
Methyl ester *a* : *b*-diacetate	+497	+405	− 92
Methyl ester *a*-benzoate	+ 74	− 27	−101
a : *b*-Diketo-acid A	+494	+427	− 67
a : *b*-Diketo-methyl ester	+507	+427	− 80

changes resulting from the oxidation of the *b*-hydroxyl group reveal the only irregularities, the probable cause of which will be discussed in a later paper.

The very marked changes in molecular rotation ($[M]_D$) on acetylation and benzoylation of the *a*-hydroxyl group, *i.e.*, −200° and −300° respectively, and acetylation of the *b*-hydroxyl group (+300°) find no parallel in any of the groups of triterpenes at present described.

As only a limited number of acidic derivatives of polyporenic acid A are known, the

decarboxy-compounds have been compared with the corresponding derivatives of the methyl ester. This is considered justifiable on the ground that, as is general with triterpene acids, $[M]_D$ does not change appreciably when the acid is esterified (cf. Barton and Jones, *loc. cit.*). Despite the presence of a carboxyl group and two hydroxyl groups the molecular-rotation differences show that the presence of hydrogen bonding between the carboxyl group or its ester and either of the hydroxyl groups in polyporenic acid A is very unlikely. Thus, in contrast to the α- and β-boswellic acids (Barton and Jones, *loc. cit.*) polyporenic acid A and its decarboxy-compound (in which hydrogen bonding involving the carboxyl group is impossible) show the same regular molecular-rotation differences. Such absence of hydrogen bonding is further evidence for the isolated nature of the functional groups in the acid. Further, the regular molecular-rotation difference (−85°) on the decarboxylation of polyporenic acid A and its derivatives shows that the process of decarboxylation does not cause any fundamental change in the polyporenic acid A skeleton (see, however, following paper).

Experimental

Rotations were determined in chloroform. M. p.s were determined on a Kofler block and are corrected unless otherwise stated. Analytical specimens were dried at a suitable temperature for 5—10 hours in a high vacuum. Alumina of activity I—II was employed for all chromatograms, and except where specified light petroleum refers to the fraction with b. p. 60—80°.

Isolation of Polyporenic Acid A from Polyporus betulinus *Fr.* (*cf.* Cross *et al.*, *loc. cit.*).—The minced fungus (204 kg.) was kept under alcohol at room temperature for 48 hours; the solvent was decanted and the fungus pressed out through muslin. The last traces of solvent were removed by means of a basket centrifuge, and the combined solutions were evaporated under reduced pressure at 30—40° until the bulk of the saponins had been deposited. Dilution with water precipitated the residual saponins, and the crude product was filtered off on muslin. The air-dried saponins were hydrolysed by 4 hours' refluxing with methanolic potassium hydroxide (15 c.c. of 5% methanolic potassium hydroxide for each g. of saponin). Then the solution was concentrated to a small bulk under reduced pressure at 30° and the residue was poured into excess of water. The non-saponifiable material was extracted with ether, and the saponified portion was saturated with salt and heated on a steam-bath to remove ether and some methanol; the impure sodium polyporenate A was deposited as a brown, granular, slightly gummy mass, which was filtered off on muslin. The air-dried salt was then digested at 30° for 2 days with sufficient glacial acetic acid to form a thick paste which was then filtered off and washed during the course of 3—4 days with acetic acid (6 × 50 c.c.) to remove most of the gummy impurities. A single crystallisation from *iso*propyl alcohol gave fine needles, m. p. 193—195° (decomp.; capillary uncorr.).

Polyporenic Acid A.—Repeated crystallisation of the impure acid, alternately from *iso*propyl alcohol and nitromethane–methanol, gave polyporenic acid A as needles, m. p. 199—200° (decomp.; preheated block), $[\alpha]_D^{20}$ +64° (*c*, 1·28 in pyridine) [Cross *et al.*, *loc. cit.*, gave m. p. 194° (capillary uncorr.), $[\alpha]_D^{20}$ +69° (*c*, 1·0 in pyridine)]. A further pure specimen of polyporenic acid A was prepared by the hydrolysis of chromatographically pure methyl ester [m. p. 148·5—149·5°, $[\alpha]_D^{20}$ +79·5° (*c*, 1·45) (see below)]. The ester (500 mg.) in methanol (10 c.c.) at 30°, was treated with cold methanolic potassium hydroxide (10 c.c.; 40%) at 20° for 72 hours. Addition of water and acidification with dilute hydrochloric acid gave a flocculent precipitate which crystallised from *iso*propyl alcohol and nitromethane–methanol giving fine needles of polyporenic acid A (300 mg.), m. p. 199—200° (decomp.; preheated block), $[\alpha]_D^{20}$ +64° (*c*, 2·2 in pyridine), $[\alpha]_D^{20}$ +74° (*c*, 0·93) (solution in chloroform was only effected by warming) (Found: C, 76·4; H, 10·1. Calc. for $C_{30}H_{48}O_4$: C, 76·2; H, 10·25%).

Methyl Polyporenate A.—The acid (10 g.) in acetone was treated with a slight excess of diazomethane in ether. Removal of the solvent and crystallisation of the residue from aqueous methanol gave stout needles (9 g.), m. p. 144—146°. A portion (500 mg.) of the product was dissolved in benzene (10 c.c.) and adsorbed on alumina (50 g.). The fraction eluted with benzene–ether (3 : 2) gave the methyl ester (380 mg.) as needles, m. p. 148·5—149·5°, $[\alpha]_D^{20}$ +79·5° (*c*, 1·45), from nitromethane–methanol (Found: C, 76·5; H, 10·4. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·4%) [Cross *et al.*, *loc. cit.*, gave m. p. 142° (capillary, uncorr.), $[\alpha]_D^{20}$ +77° (*c*, 3·0)]. A chloroform solution gave a yellow colour with tetranitromethane.

cyclo*Hexylamine Salt of Polyporenic Acid A.*—Polyporenic acid A (500 mg.) in a minimum of boiling ethyl acetate was treated with an excess of *cyclo*hexylamine, and the solution heated under

reflux for several minutes; fine needles were deposited on cooling. Recrystallisation from ethyl acetate–alcohol gave long flat needles of the *cyclo*hexylamine *salt* (490 mg.), $[\alpha]_D^{20}$ +47° (*c*, 2·06 in alcohol) (Found: N, 2·75. $C_{36}H_{61}O_4N$ requires N, 2·45%). The m. p. of this compound was characteristic though not well defined; the flat needles became opaque and serrated at 120—130°, and decomposed at 175—177°. Globules of liquid then formed and fresh needles appeared. These were most probably polyporenic acid A since complete melting took place at 190—192°.

Methyl Ester a-*Acetate*.—Acid A methyl ester (1 g.) in pyridine (6 c.c.) was treated with acetic anhydride (3 c.c.) at 20° for 72 hours, and the reaction mixture was then poured on ice. Crystallisation of the product from aqueous ethanol gave fine needles (800 mg.), m. p. 133—135°. The latter material, dissolved in benzene (20 c.c.), was adsorbed on alumina (100 g.), and the fraction eluted with benzene–ether (4 : 1) afforded *methyl polyporenate A* a-*acetate* (600 mg.), crystallising from nitromethane–methanol as long flat needles, m. p. 137—138°, $[\alpha]_D^{20}$ +33° (*c*, 1·15) (Found: C, 74·9; H, 9·75; OAc, 7·5, 7·7. $C_{33}H_{52}O_5$ requires C, 74·95; H, 9·9; OAc, 8·15%). A chloroform solution gave a yellow colour with tetranitromethane.

Methyl Ester a : b-*Diacetate*.—(*a*) Acid A methyl ester (1 g.) in glacial acetic acid (10 c.c.) and acetic anhydride (3 c.c.) was cooled below 18° and treated with 5N-anhydrous perchloric acid in acetic acid (0·1 c.c.), the temperature being kept below 35° with external cooling (cf. Whitman and Schwenk, *loc. cit.*). After 35 minutes the solution was poured on ice, and the product isolated with ether. Crystallisation from aqueous ethanol gave needles (800 mg.), m. p. 115—117°. Adsorption from benzene (20 c.c.) on alumina (100 g.) and elution with benzene–ether (9 : 1) gave *methyl polyporenate A* a : b-*diacetate* (700 mg.), which crystallised from methanol as needles, m. p. 118·5—120°, $[\alpha]_D^{20}$ +86·5° (*c*, 2·99) (Found: C, 73·85; H, 9·25; OAc, 15·4. $C_{35}H_{54}O_6$ requires C, 73·65; H, 9·55%; OAc, 15·1%). A chloroform solution gave a yellow colour with tetranitromethane.

(*b*) Acid A methyl ester *a*-acetate (500 mg.) was acetylated as in (*a*) above. The product crystallised from aqueous ethanol in needles (408 mg.), m. p. 114—115·5°. Repeated crystallisation from aqueous methanol raised the m. p. to 117—118·5° undepressed on admixture with a specimen prepared as in (*a*). This sample had $[\alpha]_D^{20}$ +87° (*c*, 1·32) (Found: C, 74·05; H, 9·8. Calc. for $C_{35}H_{54}O_6$: C, 73·65; H, 9·55%).

Hydrolysis of the Methyl Ester a : b-*Diacetate*.—The diacetate (1 g.) in methanol (20 c.c.) was treated with methanolic potassium hydroxide (20 c.c.; 20%) at 20° for 72 hours. The solution was concentrated under reduced pressure, diluted with water, and extracted with ether. Acidification and evaporation of the aqueous portion afforded a flocculent precipitate of acid (600 mg.). Several crystallisations from *iso*propyl alcohol yielded fine needles, m. p. 198—199° (decomp.; preheated block) undepressed on admixture with an authentic specimen of polyporenic acid A, $[\alpha]_D^{20}$ +63° (*c*, 1·3 in pyridine).

Methyl Ester a-*Benzoate*.—Acid A methyl ester (2 g.) in pyridine (12 c c.) was treated with benzoyl chloride (1·4 g.) at 0°, and the mixture set aside at 20° for 48 hours. It was then poured on ice, and the product isolated. Crystallisation from aqueous methanol gave *methyl polyporenate A* a-*benzoate* (1·8 g.) as stout blunt needles, m. p. 139—140° raised by repeated crystallisation from methanol to 142—143°, $[\alpha]_D^{20}$ +12·5° (*c*, 1·84) (Found: C, 77·55, 77·1; H, 9·15, 9·3. $C_{38}H_{54}O_5$ requires C, 77·25; H, 9·2%).

Hydrolysis. The benzoate (250 mg.) was hydrolysed with methanolic potassium hydroxide (20%) at 20° for 72 hours. The acidic product (150 mg.), isolated as described above, crystallised from *iso*propyl alcohol as fine needles of polyporenic acid A, m. p. and mixed m. p. 198—199° (decomp.; preheated block).

Chromium Trioxide Oxidising Reagent.—A cold solution of chromium trioxide (266·7 g.) in concentrated sulphuric acid (230 c.c.) and distilled water (400 c.c.) was made up to 1 l. This solution is 8N with respect to oxygen. The compound to be oxidised was dissolved in a minimum of pure acetone (distilled over potassium permanganate) at 20°, and the reagent added dropwise from a microburette until an orange-brown colour persisted. External cooling was applied to keep the temperature below 30°.

a : b-*Diketopolyporenic Acid A*.—Acid A (500 mg.) was treated with chromium trioxide solution (0·57 c.c.; theory for 4 equivs., 0·53 c.c.) and set aside for 30 minutes. Dilution with water caused the product to crystallise. Three crystallisations from methanol gave the a : b-*diketopolyporenic acid A* (390 mg.) as stout needles, m. p. 206·5—207·5° (decomp.; preheated block), $[\alpha]_D^{20}$ +105·5° (*c*, 1·05), $[\alpha]_D^{20}$ + 103·5° (*c*, 3 in pyridine) (Found: C, 77·2, 77·15; H, 9·55, 9·7. $C_{30}H_{44}O_4$ requires C, 76·9; H, 9·45%). The diketone readily formed a gelatinous 2 : 4-dinitrophenylhydrazone.

a-*Oxime*. The diketo-acid (500 mg.) in ethanol (3 c.c.) was boiled for 5 hours with hydroxylamine hydrochloride (200 mg.) and fused sodium acetate (500 mg.). The product, isolated by addition of water to the cold solution, was repeatedly crystallised from aqueous ethanol giving a : b-*diketopolyporenic acid A* a-*oxime* as stout prismatic needles, m. p. 212—214° (decomp.; preheated block), $[\alpha]_D^{20}$ +34° (*c*, 1·49) (Found : C, 74·35; H, 9·4; N, 2·9. $C_{30}H_{45}O_4N$ requires C, 74·5; H, 9·4; N, 2·9%).

Methyl a : b-*Diketopolyporenate A*.—(*a*) Methyl polyporenate A (500 mg.) was oxidised with chromium trioxide solution (0·55 c.c.; theory for 4 equivs., 0·52 c.c.). After 30 minutes water was added. *Methyl* a : b-*diketopolyporenate A* (340 mg.) formed stout needles (from methanol), m. p. 129—130°, $[\alpha]_D^{20}$ +106° (*c*, 0·89) (Found : C, 76·85, 77·45; H, 9·5, 9·8. $C_{31}H_{46}O_4$ requires C, 77·1; H, 9·6%).

(*b*) *a* : *b*-Diketo-acid A (200 mg.) was treated with a slight excess of diazomethane in ether. Evaporation of the solvent gave a gum which crystallised from methanol as stout needles (160 mg.), m. p. 126—127°, which was raised by repeated crystallisation from methanol to 129—130°, undepressed on admixture with a specimen prepared as in (*a*), $[\alpha]_D^{20}$ +105° (*c*, 1·37). The diketone readily formed a gelatinous 2 : 4-dinitrophenylhydrazone.

a-*Oxime*. (*a*) Methyl *a* : *b*-diketopolyporenate A (250 mg.) in ethanol (1·5 c.c.) was boiled for 5 hours with hydroxylamine hydrochloride (100 mg.) and fused sodium acetate (250 mg.). Dilution with water and filtration yielded a product which was crystallised several times from aqueous ethanol and ethanol, giving *methyl* a : b-*diketopolyporenate A* a-*oxime* as fine needles, m. p. 159—160° (capillary; uncorr.), remelting at 170—171° if the melt was allowed to cool and solidify. A specimen dried for analysis had m. p. 163—164° remelting at 168—169° (Found: C, 74·3; H, 9·4; N, 2·8. $C_{31}H_{47}O_4N$ requires C, 74·8; H, 9·5; N, 2·8%).

(*b*) Methyl *a* : *b*-diketopolyporenate A (250 mg.) and hydroxylamine hydrochloride (250 mg.) in pyridine (0·25 c.c.) and ethanol (2·5 c.c.) were heated under reflux for 15 hours. The product, isolated in the usual way and crystallised several times from aqueous alcohol, gave the *a*-oxime as long hairlike needles, m. p. 163—164°, remelting at 169—170° [the m. p. was undepressed on admixture with a specimen prepared as in (*a*)], $[\alpha]_D^{20}$ +59° (*c*, 0·96) (Found : C, 74·7; H, 9·6; N, 2·95. Calc. for $C_{31}H_{47}O_4N$: C, 74·8; H, 9·5; N, 2·8%).

Methyl b-*Ketopolyporenate A* a-*Acetate*.—Methyl polyporenate A *a*-acetate (500 mg.) was oxidised with chromium trioxide solution (0·27 c.c.; theory for 2 equivs., 0·24 c.c.) in the usual way. The product was crystallised from methanol giving *methyl* b-*ketopolyporenate A* a-*acetate* as stout needles (350 mg.), m. p. 159·5—161°, raised by repeated crystallisation from methanol and ethanol to 162—163°, $[\alpha]_D^{20}$ +45° (*c*, 1·2) (Found : C, 75·55; H, 9·8. $C_{33}H_{50}O_5$ requires C, 75·25; H, 9·55%). Light absorption in alcohol : Max. 2900 Å; $\varepsilon = 270$. The compound did not form a 2 : 4-dinitrophenylhydrazone or an oxime.

Methyl b-*Ketopolyporenate A* a-*Benzoate*.—Methyl polyporenate A *a*-benzoate (500 mg.) was oxidised with chromium trioxide solution (0·25 c.c.; theory for 2 equivs., 0·21 c.c.) at 25°. After 30 minutes water was added and the product isolated. Several crystallisations from methanol gave *methyl* b-*ketopolyporenate A* a-*benzoate* (320 mg.) as long flat needles, m. p. 103—104°, $[\alpha]_D^{20}$ +25° (*c*, 1·8) (Found : C, 77·2; H, 8·8. $C_{38}H_{52}O_5$ requires C, 77·5; H, 8·9%). The ketone did not form a 2 : 4-dinitrophenylhydrazone or an oxime.

b-*Ketopolyporenic Acid A*.—Methyl *b*-ketopolyporenate A *a*-acetate (450 mg.) in methanol (25 c.c.) was treated with methanolic potassium hydroxide (25 c.c.; 20%) for 72 hours at 20°. The yellow solution was diluted with water and extracted with ether. Acidification of the aqueous portion and removal of ether and some methanol under reduced pressure yielded a flocculent precipitate of acid (350 mg.). Repeated crystallisation from aqueous *iso*propyl alcohol and aqueous methanol gave b-*ketopolyporenic acid A* as blunt needles, m. p. 202—204° (decomp.; preheated block), $[\alpha]_D^{20}$ +77·5° ± 2° (*c*, 0·72, 1·07) (Found : C, 76·45; H, 9·75). $C_{30}H_{44}O_4$ requires C, 76·55; H, 9·85%). Light absorption in alcohol : Max. 2920—2930 Å; $\varepsilon = 450$.

Methyl b-*Ketopolyporenate A*.—*b*-Keto-acid A (500 mg.) was treated with a slight excess of diazomethane in ether. Removal of the solvent and repeated crystallisation of the product from aqueous methanol gave *methyl* b-*ketopolyporenate A* as silky needles, m. p. 160—161·5°, $[\alpha]_D^{20}$ +76·5° ± 1° (*c*, 0·59, 1·42) (Found: C, 77·15; H, 10·0. $C_{31}H_{48}O_4$ requires C, 76·8; H, H, 10·0%).

Oxidation of Methyl b-*Ketopolyporenate A*.—The ester (60 mg.) was oxidised in the usual manner. The product, after several crystallisations from methanol, afforded methyl *a* : *b*-diketopolyporenate A (35 mg.) as stout needles, m. p. and mixed 128—129°.

Decarboxylation of Polyporenic Acid A.—Polyporenic acid A (269 mg.), recrystallised eight times from *iso*propyl alcohol and dried for 4 hours at 100°/0·05 mm., was heated for 80 minutes

at 220° in a slow stream of pure dry nitrogen. The issuing gases were passed through an absorption train, and carbon dioxide (25·3 mg.), but no water, was absorbed (theory: CO_2 for one carboxyl group, 25·1 mg.). Polyporenic acid A (1 g.) was decarboxylated at 200—220° in an inert atmosphere, the residual clear brittle resin dissolved in ether, and the solution washed with 5% aqueous methanolic alkali, dilute hydrochloric acid, and water and dried. Evaporation yielded a solid which was excessively soluble in all solvents except light petroleum (b. p. 40—60°) and nitromethane. A single crystallisation from light petroleum (b. p. 40—60°) gave hair-like needles (700 mg.), m. p. 142—145°, raised by repeated crystallisation from nitromethane containing a trace of methanol to 148—150°, $[\alpha]_D^{20}$ +68° (*c*, 1·1). The crude decarboxylated material (900 mg.) was dissolved in benzene (25 c.c.) and adsorbed on alumina (90 g.). Elution with benzene–ether (9 : 1) gave the *decarboxy-compound* (650 mg.), m. p. 149—152°, which afforded long flat needles (from nitromethane), m. p. 151—153°, $[\alpha]_D^{20}$ +69° (*c*, 2·6) (Found: C, 81·55; H, 11·25. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%). A solution in chloroform gave a yellow colour with tetranitromethane.

a-*Acetate of Decarboxy-compound*.—The decarboxy-compound (500 mg.) in pyridine (4 c.c.) was treated with acetic anhydride (2 c.c.) at 20° for 72 hours. The uncrystallisable product was adsorbed on alumina (50 g.) from light petroleum–benzene (5 : 1; 20 c.c.). Elution with light petroleum–benzene (3 : 2) gave the a-*acetate* (420 mg.), as long needles (from methanol), m. p. 154—155·5°, $[\alpha]_D^{20}$ +22° (*c*, 2·92) (Found: C, 79·2; H, 10·6. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). A chloroform solution gave a yellow colour with tetranitromethane.

a : b-*Diacetate of Decarboxy-compound*.—The decarboxy-compound (750 mg.) in acetic anhydride (6 c.c.) was heated under reflux for 1 hour with fused sodium acetate (250 mg.). The product, isolated in the usual way, was dissolved in light petroleum–benzene (4 : 1; 20 c.c.) and adsorbed on alumina (70 g.). The fraction eluted with light petroleum–benzene (2 : 3) crystallised from methanol and ethanol giving the a : b-*diacetate* (455 mg.) as flat needles, m. p. 115—116°, $[\alpha]_D^{20}$ +79° (*c*, 2·67) (Found C, 77·0; H, 10·0. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·25%).

a-*Benzoate of Decarboxy-compound*.—The decarboxy-compound (500 mg.) in pyridine (6 c.c.) was treated with benzoyl chloride (0·5 c.c.) at 0°, and set aside at 0° for 24 hours and at 20° for a further 24 hours. The product, isolated in the usual way, was dissolved in light petroleum–benzene (3 : 2; 25 c.c.) and adsorbed on alumina (50 g.). Elution with light petroleum–benzene (1 : 4) gave the a-*benzoate* (250 mg.), as stout needles (from ethanol), m. p. 166—167°, $[\alpha]_D^{20}$ −5° (*c*, 1·71) (Found: C, 81·15; H, 10·0. $C_{36}H_{52}O_3$ requires C, 81·15; H, 9·85%).

Decarboxy-a : b-*diketo-compound*.—(*a*) *a* : *b*-Diketo-acid A (1 g.) was decarboxylated at 210—220° in an inert atmosphere for 1·5 hours. The cold melt, which solidified on treatment with methanol, was crystallised several times from methanol giving the *decarboxy*-a : b-*diketo*-compound (500 mg.) as plates, m. p. 148—149° raised by repeated crystallisation from methanol–chloroform to 150—151°, $[\alpha]_D^{20}$ +100° (*c*, 2·23) (Found: C, 82·0; H, 10·2. $C_{29}H_{44}O_2$ requires C, 82·05; H, 10·45%). The diketone readily formed a gelatinous 2 : 4-dinitrophenylhydrazone.

(*b*) Decarboxylated acid A (250 mg.) was oxidised with chromium trioxide solution (0·60 c.c.; theory, 0·55 c.c.). The diketone, isolated in the usual way, crystallised from methanol and ethanol as plates, m. p. 149—150° undepressed on admixture with a specimen prepared as in (*a*), $[\alpha]_D^{20}$ +100° (*c*, 0·93).

a-*Oxime*.—The decarboxy-*a* : *b*-diketo-compound (500 mg.) and hydroxylamine hydrochloride (500 mg.) in pyridine (0·5 c.c.) and ethanol (5 c.c.) were heated under reflux for 18 hours. The product, which crystallised on cooling, was isolated by dilution with water and filtration. Several crystallisations from methanol–chloroform and ethanol gave fine needles of the a-*oxime*, m. p. 199—200°, $[\alpha]_D^{20}$ +34·5° (*c*, 2·79) (Found: C, 79·2; H, 10·5; N, 3·55. $C_{29}H_{45}O_2N$ requires C, 79·2; H, 10·3; N, 3·2).

Lithium Aluminium Hydride Reduction of Acid A Methyl Ester.—Methyl polyporenate A (900 mg.) in a minimum of dry ether was stirred at 0° and an excess of an ethereal solution of lithium aluminium hydride (16 c.c.; 0·48M) was added dropwise. After 15 minutes water was added to decompose excess of reagent, and dilute sulphuric acid (20 c.c.; 10%) to decompose the metal complex. The ethereal solution was washed thoroughly with dilute sulphuric acid, sodium hydrogen carbonate solution and water, dried, and evaporated. The residue was crystallised from nitromethane or aqueous methanol giving small prisms of the *triol* (650 mg.), m. p. 172—173·5°, $[\alpha]_D^{20}$ +65° (*c*, 3·42) (Found: C, 78·45; H, 10·7. $C_{30}H_{50}O_3$ requires C, 78·55; H, 11·0%). A chloroform solution gave a yellow colour with tetranitromethane. On titration with perbenzoic acid in chloroform solution the triol had consumed 1·98 equivs. when the uptake of oxidant was complete.

Oxidation of the Triol.—The triol (650 mg.) was carefully oxidised with a slight excess of chromium trioxide solution. Crystallisation of the product from methanol gave *a* : *b*-diketo-polyporenic acid A, m. p. and mixed m. p. 205—206°, $[\alpha]_D^{20}$ +104° (*c*, 1·06).

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93. *The Chemistry of the Triterpenes. Part XIV.* Further Evidence concerning the Unsaturated Centres of Polyporenic Acid A.*

By E. R. H. Jones and Gilbert F. Woods.

Polyporenic acid A contains two double bonds one of which readily undergoes catalytic hydrogenation yielding two non-interconvertible series of dihydro-derivatives. The readily reducible double bond is present in a vinylidene group and the inert double bond is most probably of the tetra-substituted type. In contrast to the parent acid the stereoisomeric dihydro-acids do not decarboxylate, indicating that the reactive double bond is $\beta\gamma$ to the carboxyl group in polyporenic acid A.

In the original investigation of polyporenic acid A (Cross, Eliot, Heilbron, and Jones, *J.*, 1940, 632), the presence of two double bonds was indicated by a microhydrogenation and by per-acid titrations, confirmed in the preceding paper. Although the acid reacted with 2 mols. of hydrogen under the vigorous conditions of a microhydrogenation at 95°, hydrogenation at 20° resulted in the uptake of only 1 mol. of hydrogen (Cross and Jones, *J.*, 1940, 1491). This procedure resulted in the isolation and characterisation of what was believed to be the dihydro-derivative of polyporenic acid A. Comparative ozonolysis experiments on a derivative of the latter and on the parent compound, from which yields of formaldehyde of 4% and 50% respectively were obtained, indicated that the readily reducible double bond was present as a vinylidene group.

The hydrogenation of acid A has now been studied in greater detail and chromatographic examination of the methyl esters and methyl ester acetates has revealed that the process is more complicated than was originally believed. The product of hydrogenation of the acid itself had the same physical constants as described by Cross and Jones (*loc. cit.*), although it proved to be dimorphous. Esterification of this acid or hydrogenation of methyl polyporenate A, gave, after repeated crystallisation, an ester with the properties described earlier. By careful chromatography this material yielded two isomeric compounds, m. p.s 159—160° and 132—133°, and more of the latter was isolated by chromatographic purification of the material contained in the initial mother liquors. Further experiments involving the catalytic hydrogenation of the methyl ester *a*-acetate and *a* : *b*-diacetate, and acetylation of the mixed methyl dihydro-esters also indicated the existence of two methyl dihydro-esters in both the monoacetate and the diacetate series. The results of these initial experiments were somewhat unpredictable and difficult to repeat. However, the possibility of polymorphism was ruled out in all cases by the separation of one and the same compound even when its solutions were seeded with the other isomer.

Further study of these reactions with careful chromatographic purification of the products conclusively established the existence of two non-interconvertible series of dihydro-derivatives. These have been arbitrarily designated (I) and (II), compounds in series

* Part XIII, preceding paper.

(I) exhibiting higher melting points and lower rotations than their isomers in series (II). It has not been possible to separate the mixture of parent dihydro-acids, but the mixed isomers exist in two polymorphic forms.

The infra-red absorption spectra of methyl dihydro-(I)-polyporenate A *a* : *b*-diacetate (m. p. 137·5—139°, $[\alpha]_D$ + 80°) and methyl dihydro-(II)-polyporenate A *a* : *b*-diacetate (m. p. 116·5—117·5°, $[\alpha]_D$ + 87°) were compared. The two compounds displayed identical absorption curves in carbon disulphide solutions, but there were significant minor differences when the compounds were examined in the crystalline state (Nujol suspension). The identical solution spectra obviously preclude structural isomerism and any but minor stereochemical differences. The latter become apparent in the divergent spectra of the crystalline samples; the characteristic ester group absorptions at 1000—1050 cm.$^{-1}$ and 1150—1200 cm.$^{-1}$ are those revealing the greatest differences. This may be due to the close spacial proximity between the methyl group produced in the hydrogenation and the carboxylic ester group (see below).

The second double bond in polyporenic acid A is inert towards catalytic hydrogenation under normal conditions and is almost certainly cyclic. It does not migrate in the presence of hydrogen and a catalyst in an acidic medium (cf. 'α'-spinasterol; Fieser, Fieser, and Chakravarti, *J. Amer. Chem. Soc.*, 1949, **71**, 2226), since the same product was isolated from the hydrogenation of acid A, by employing a platinum catalyst, in both acidic and neutral media.

The infra-red spectra of a number of derivatives of polyporenic acid A have been examined. In solution (chloroform) and in the solid state (Nujol suspension), methyl polyporenate A and *a* : *b*-diketopolyporenic acid A display prominent bands at 902 and 1648 cm.$^{-1}$ which are absent in the epimeric methyl dihydro-ester diacetates as well as in the decarboxy-*a* : *b*-diketo-compound (see preceding paper), and are attributed to the vinylidene group, $CH_2{=}C<$. This group clearly disappears when *a* : *b*-diketopolyporenic acid A is decarboxylated to the decarboxy-*a* : *b*-diketo-compound which shows no bands at 902 and 1648 cm.$^{-1}$. Methyl polyporenate A and its derivatives display no marked absorption in the 650—850 cm.$^{-1}$ range, and the presence of cyclic —CH=CH— or —CH=C< groups is therefore highly improbable. The second double bond would appear to be of the tetrasubstituted type.

Oxidation of the *b*-hydroxyl group in methyl polyporenate A *a*-acetate gives rise to a carbonyl group which does not react with the usual carbonyl group reagents (previous paper), but for which evidence is obtained by infra-red examination. Thus, besides the carboxyl frequency at 1736 cm.$^{-1}$, crystalline *a* : *b*-diketopolyporenic acid A gives rise to two strong ketonic carbonyl bands at 1710 and 1692 cm.$^{-1}$ which, in solution, appear as a single strong band at 1713 cm.$^{-1}$ in both the *a* : *b*-diketo-acid and its decarboxy-derivative. Further, the ester groups in methyl polyporenate A *a*-acetate display a single strong band at 1729 cm.$^{-1}$ which is also present in methyl *b*-ketopolyporenate A *a*-acetate. However, instead of the hydroxylic absorption of the former at 3500 cm.$^{-1}$ the latter displays a second strong band at 1708 cm.$^{-1}$ which must be attributed to the newly introduced carbonyl group. It may be noted that the values recorded above for the two ketonic carbonyl frequencies exclude the possibility of either group being present in a five-membered ring (cf., Jones, Williams, Whalen, and Dobriner, *J. Amer. Chem. Soc.*, 1948, **70**, 2024).

Further to the observation that polyporenic acid A readily decarboxylates when melted (preceding paper) it has been found that the dihydro-acid is unaffected after being kept in a molten state for some considerable time. The infra-red absorption-spectra bands displayed by polyporenic acid A at 902 and 1648 cm.$^{-1}$, attributable to the vinylidene group, disappear on both hydrogenation and decarboxylation of the acid. It is clear, therefore, that the close spatial proximity between the unsaturated methylene group and the carboxyl group must be responsible for the decarboxylation, and moreover in the absence of selective absorption characteristic of an $\alpha\beta$-unsaturated acid it must be concluded that polyporenic acid A contains the double bond $\beta\gamma$ to the carboxyl group.

It is well known that $\beta\gamma$-unsaturated acids readily decarboxylate when heated and that the elimination of carbon dioxide is accompanied by a shift of the double bond to the former $\alpha\beta$-position (cf. Arnold, Elmer, and Dodson, *J. Amer. Chem. Soc.*, 1950, **72**, 4359).

Barton and Brooks (*J.*, 1951, 257) have shown that the triterpenoid morolic acid loses carbon dioxide when melted, producing oleanol in excellent yield. The decarboxylation of polyporenic acid A is analogous to that of morolic acid except that in the former the reacting centres are almost certainly located in a side-chain. The infra-red spectrum of the decarboxy-compound displays a band of medium strength at 815 cm.$^{-1}$, not shown by the parent acid, which is indicative of the presence of a trisubstituted double bond (cf. Bladon, Fabian, Henbest, Koch, and Wood, *J.*, 1951, 2402), formed as the result of migration during decarboxylation.

Analysis of all the available analytical data shows unequivocally that polyporenic acid A is tetracyclic. Of 34 analyses of the acid and its derivatives, 22 agree within the usual limits with a C_{29}, 30 with a C_{30}, and 19 with a C_{31} formula for acid A. The evidence is thus somewhat in favour of $C_{30}H_{48}O_4$. As indicated in the preceding paper, however, equivalent-weight determinations gave results in good agreement with a C_{31} formula (Cross, Eliot, Heilbron, and Jones, *loc. cit.*). Furthermore, an *X*-ray crystallographic examination of the methyl ester failed to distinguish between the C_{30} and C_{31} formulæ for the acid. The molecular weight observed (496±8) slightly favours $C_{32}H_{52}O_4$ (M=501) for methyl polyporenate A. Attempts to prepare a pure derivative containing sufficient halogen to be of value in establishing the empirical formula of the acid by microanalysis have not yet been successful.

The molecular rotation differences consequent upon hydrogenation of the reactive double bond in polyporenic acid A are shown in the Table. In neither series is there any great change in [M]. Barton and Jones (*J.*, 1944, 659) have pointed out that the tetracyclic triterpenes containing reactive double bonds form a single group, the members of which show little change in [M] on hydrogenation. In this respect polyporenic acid A fits into the group.

	[M]				
Compound	Parent	Dihydro- (I)-	Dihydro- (II)-	Δ_I	Δ_{II}
Polyporenic acid A	+303° (pyr.)	+313° (pyr.) *			+10°
Methyl ester	+386	+374°	+379°	−12°	− 7°
Methyl ester *a*-acetate	+175	+170	+207	− 5	+32
Methyl ester *a* : *b*-diacetate ...	+497	+458	+498	−39	+ 1

* Mixed dihydro-acids.

Δ_I = [M], dihydro-(I)- − [M], parent. Δ_{II} = [M], dihydro-(II)- − [M], parent.

Experimental

Rotations were determined in chloroform. M. p.s were determined on a Kofler block and are corrected unless otherwise stated. Analytical specimens were dried at a suitable temperature for 5—10 hours in a high vacuum. Alumina of activity I—II was employed for all chromatograms and except where specified, light petroleum refers to the fraction, b. p. 60—80°.

Hydrogenation of Polyporenic Acid A.—Polyporenic acid A (10 g.) in glacial acetic acid (150 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of Adams's catalyst (50 mg.). The absorption of hydrogen was rapid and ceased when one mol. had been taken up. The product crystallised from aqueous acetic acid as needles (7·4 g.), m. p. 216—218° (Found : C, 75·8; H, 10·55. Calc. for $C_{30}H_{50}O_4$: C, 75·9; H, 10·6%). Recrystallisation from methanol–light petroleum (1 : 1) or methanol–chloroform gave fine needles, m. p. 222—224°. Recrystallisation of the latter from aqueous acetic acid again gave the low-melting form; the mixed m. p. of the two forms was 216—220°. Both forms had $[\alpha]_D^{20}$ +66° (*c*, 0·4 in pyridine). [Cross and Jones, *loc. cit.*, gave m. p. 216° (capillary uncorr.), $[\alpha]_D^{20}$ +66° (*c*, 1·1 in pyridine) for dihydropolyporenic acid A.] It is now considered that this material is a mixture of two stereoisomers and that the mixture is dimorphous, both crystalline forms having the same heterogeneous composition.

Esterification of the Product from the Hydrogenation of Polyporenic Acid A.—The above dihydro-product (600 mg.) was esterified with diazomethane. The ester crystallised from aqueous acetic acid as needles (470 mg.), m. p. 140—144°, raised by repeated crystallisation from aqueous methanol to 145—148°, $[\alpha]_D^{20}$ +77° (*c*, 1·24) (cf. below).

Hydrogenation of Methyl Polyporenate A.—The ester (2·5 g.) in acetic acid (40 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of Adams's catalyst

(30 mg.). One mol. of hydrogen was rapidly taken up. The product crystallised from aqueous ethanol as rosettes of needles (2 g.), m. p. 132—134°. Repeated crystallisation from aqueous ethanol and aqueous methanol gave needles (700 mg.) with constant m. p., 144—147°, $[\alpha]_D^{20}$ +78° (*c*, 1·81). A mixed m. p. with a specimen prepared as above was 144—147°. [Cross and Jones, *loc. cit.*, gave m. p. 142° (capillary uncorr.), $[\alpha]_D^{20}$ +76° (*c*, 1·0), for methyl dihydropolyporenate A.]

Hydrolysis of the Product from the Hydrogenation of Methyl Polyporenate A.—The dihydro-ester (100 mg.), m. p. 144—147°, was hydrolysed with methanolic potassium hydroxide (15%) at 20° for 72 hours. The acidic product (70 mg.) was isolated in the usual way, and two crystallisations from methanol gave fine needles of the mixed dihydro-acids, m. p. 222—224°, $[\alpha]_D^{20}$ +65·5° (*c*, 1·06 in pyridine).

Methyl Dihydro-I-polyporenate A.—The product (700 mg.), m. p. 144—147°, from the hydrogenation of acid A methyl ester, was dissolved in a minimum of light petroleum–benzene (1 : 1) and adsorbed on alumina (70 g.). The fraction (60 mg.) eluted with benzene–ether (2 : 1) (100 c.c.) crystallised from nitromethane as prismatic needles, m. p. 132—133°, which were identical with methyl dihydro-II-polyporenate A (see below). The fraction (200 mg.) eluted with benzene–ether (1 : 1) (200 c.c.) crystallised from aqueous methanol as a mixture of prisms and needles, m. p. 136—151°. Finally, further elution with benzene–ether (1 : 1) (800 c.c.) gave a fraction (400 mg.) which crystallised from methanol giving *methyl dihydro-I-polyporenate A* as stout needles, m. p. 159—160°, $[\alpha]_D^{20}$ +76·5° (*c*, 1·19) (Found: C, 75·9; H, 10·7. $C_{31}H_{52}O_4$ requires C, 76·15; H, 10·75%). A chloroform solution gave a faint yellow colour with tetranitromethane.

Methyl Dihydro-II-polyporenate A.—Evaporation of the mother liquors from the first three crystallisations of the product from the hydrogenation of acid A methyl ester yielded a gummy solid, m. p. 125—130°, which was exceedingly soluble and crystallised with difficulty. The solid (2 g.) in benzene (30 c.c.) was adsorbed on alumina (160 g.). The fraction eluted with ether was crystallised from nitromethane–methanol giving *methyl dihydro-II-polyporenate A* (1 g.) as prismatic needles, m. p. 132—133° undepressed on admixture with the specimen described above, $[\alpha]_D^{20}$ +77·5° (*c*, 2·8) (Found: C, 76·15; H, 10·85. $C_{31}H_{52}O_4$ requires C, 76·15; H, 10·75%). A chloroform solution gave a faint yellow colour with tetranitromethane. Further elution gave a number of gummy fractions (600 mg.) which could not be inducted to crystallise. The remaining material (400 mg.) was not eluted with methanol, and may have been hydrolysed.

Methyl Dihydro-I-polyporenate A a-*Acetate.*—(*a*) The product (1·5 g.), m. p. 145—147°, from the hydrogenation of acid A methyl ester, was acetylated in pyridine at 20° in the usual manner. The product crystallised from methanol as needles (760 mg.), m. p. 172—174°; chromatographic purification of these gave *methyl dihydro-I-polyporenate A* a-*acetate* as blunt needles, m. p. 176—178°, $[\alpha]_D^{20}$ +32° (*c*, 3·9) (Found: C, 74·6; H, 10·0. $C_{33}H_{54}O_5$ requires C, 74·7; H, 10·25%).

(*b*) The dihydro-I-acid methyl ester (100 mg.), acetylated in the same way, gave methyl dihydro-I-polyporenate A *a*-acetate (60 mg.) as needles, m. p. 176—178° undepressed on admixture with a specimen prepared as above. A chloroform solution gave a faint yellow colour with tetranitromethane.

Methyl Dihydro-II-polyporenate A a-*Acetate.*—The dihydro-II-acid methyl ester (500 mg.) in pyridine was acetylated as above. Crystallisation of the product from aqueous methanol yielded needles of *methyl dihydro-II-polyporenate A* a-*acetate* (400 mg.), m. p. 155—157°, raised by repeated crystallisation from methanol and ethanol to 158·5—159·5°, $[\alpha]_D^{20}$ +39° (*c*, 1·15) (Found: C, 75·0; H, 10·2. $C_{33}H_{54}O_5$ requires C, 74·7; H, 10·25%). A chloroform solution gave a faint yellow colour with tetranitromethane.

Methyl Dihydro-I-polyporenate A a : b-*Diacetate.*—(*a*) The dihydro-(I)-acid methyl ester *a*-acetate (600 mg.) was further acetylated by Whitman and Schwenks's method (*J. Amer. Chem. Soc.*, 1946, **68**, 1865). Crystallisation of the product from aqueous methanol gave *methyl dihydro-I-polyporenate A* a : b-*diacetate* (410 mg.) as blunt needles, m. p. 137—139°, $[\alpha]_D^{20}$ +80·5° (*c*, 1·80) (Found: C, 73·4; H, 9·65. $C_{35}H_{56}O_6$ requires C, 73·4; H, 9·85%). A chloroform solution gave a faint yellow colour with tetranitromethane.

(*b*) The dihydro-I-acid methyl ester (100 mg.) was acetylated as in (*a*) above, giving methyl dihydro-I-polyporenate A *a* : *b*-diacetate as blunt needles (from aqueous methanol), m. p. 137·5—139° undepressed on admixture with a specimen prepared as above, $[\alpha]_D^{20}$ +80° (*c*, 3·3). On titration with perbenzoic acid in chloroform solution methyl dihydro-I-polyporenate A *a* : *b*-diacetate had consumed 1·16 equiv. when the uptake of per-acid was complete.

Methyl Dihydro-II-polyporenate A a : b-*Diacetate.*—(*a*) Methyl polyporenate A *a* : *b*-diacetate

(2 g.) in acetic acid (60 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of Adams's catalyst (30 mg.) until sufficient hydrogen to saturate one double bond had been taken up. After filtration of the catalyst and removal of the solvent, crystallisation of the residue from aqueous ethanol gave needles (1·6 g.), m. p. 112—114°. This latter material (1 g.) was adsorbed from light petroleum–benzene (1 : 1; 30 c.c.) on alumina (100 g.). Elution with benzene and crystallisation of the eluate from aqueous ethanol gave *methyl dihydro-II-polyporenate A* a : b-*diacetate* (460 mg.) as blunt needles, m. p. 116·5—117·5°, $[\alpha]_D^{20}$ +85° (*c*, 1·86) (Found: C, 73·2; H, 9·65. $C_{35}H_{56}O_6$ requires C, 73·4; H, 9·85%). A chloroform solution gave a faint yellow colour with tetranitromethane. The remaining material (450 mg.) eluted from the column melted over a considerable range.

(*b*) Methyl dihydro-II-polyporenate A *a*-acetate (175 mg.), m. p. 158—159°, was further acetylated in the presence of perchloric acid. Crystallisation of the product from aqueous methanol gave methyl dihydro-II-polyporenate A *a* : *b*-diacetate (120 mg.) as elongated prisms, m. p. 114—116°, raised by several crystallisations from aqueous methanol and methanol to 116·5—117·5°, which was undepressed on admixture with a specimen as prepared in (*a*); $[\alpha]_D^{20}$ +89° (*c*, 4·24).

(*c*) Methyl dihydro-II-polyporenate A (300 mg.), was acetylated as in (*b*). The product isolated in the usual way and crystallised several times from aqueous methanol gave blunt needles of methyl dihydro-II-polyporenate A *a* : *b*-diacetate (200 mg.), m. p. 116—117·5° undepressed on admixture with specimens prepared as in (*a*) and (*b*), $[\alpha]_D^{20}$ +87° (*c*, 3·26).

Attempted Decarboxylation of the Product from the Hydrogenation of Polyporenic Acid A.— Mixed dihydro-acids A (256 mg.), m. p. 216—218°, dried for 6 hours at 130°/0·05 mm., were heated for 45 minutes at 225—230° in an inert atmosphere. No carbon dioxide or water was eliminated. The residue crystallised from aqueous acetic acid as fine needles (200 mg.; 78% recovery), m. p. 214—216°, undepressed on admixture with the starting material.

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94. *The Chemistry of the Triterpenes. Part XV.* The Environment of the Unreactive Double Bond of Polyporenic Acid A.*

By T. G. HALSALL, E. R. H. JONES, and A. J. LEMIN.

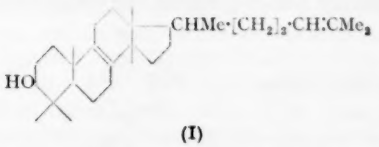
Oxidation of derivatives of methyl polyporenate A has given products containing characteristic chromophoric systems. Detailed examination of these compounds has permitted the elucidation of the environment of the unreactive double bond and the formulation of a partial structure for polyporenic acid A. A close relationship exists between this partial structure and the structure now proposed for lanosterol; it is emphasized by the isolation of 1 : 2 : 8-trimethylphenanthrene from the selenium dehydrogenation products from polyporenic acid A.

The unreactive hydroxyl group has been shown to be in the β-position to the inert double bond.

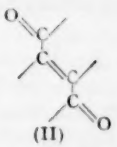
IN the preceding two papers polyporenic acid A has been characterised as a tetracyclic dihydroxy-carboxylic acid with two double bonds. One of these has been shown to be present in a vinylidene group, and to be in the βγ-position to the carboxyl group. The other is unreactive and the infra-red spectra of derivatives of polyporenic acid A indicate that it is fully substituted. In other non-steroid tetracyclic compounds an unreactive tetrasubstituted double bond has also been found and has been shown to lie between two rings as in lanosterol (I) (Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142; Barton, Fawcett, and Thomas, *J.*,

* Part XIV, preceding paper.

1951, 3147; Voser, Montavon, Gunthard, Jeger, and Ruzicka, *Helv. Chem. Acta*, 1950, **33**, 1893; Curtis, Fridricksons, and Mathieson, *Nature*, 1952, **170**, 321).



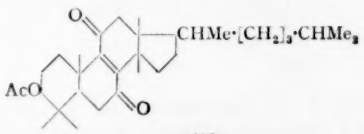
(I)



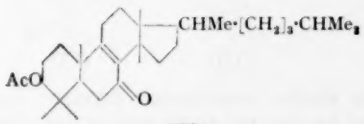
(II)

In lanosterol the environment of the unreactive double bond has been elucidated largely by a study of the behaviour of lanostenyl acetate on oxidation. A similar study of the oxidation of derivatives of polyporenic acid A has now been carried out.

Oxidation of methyl polyporenate A *a* : *b*-diacetate with chromic acid in acetic acid gave a diketone (methyl *c* : *d*-diketopolyporenate A *a* : *b*-diacetate), $C_{35}H_{50}O_8$, the ultra-violet spectrum of which showed a maximum at 2730 Å characteristic of the system (II) in the fully transoid arrangement. Similar light-absorption properties are shown by 8 : 11-diketolanost-9-en-2-yl acetate (III) (Cavalla and McGhie, *J.*, 1951, 834). The formula of the diketone indicated that the reactive double bond was still present and this was confirmed by the presence of a band at 900 cm.$^{-1}$ in the infra-red spectrum of the diketone determined in carbon tetrachloride.



(III)



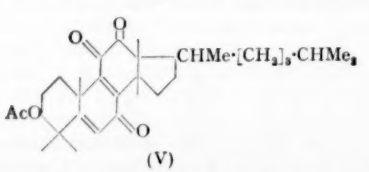
(IV)

Similar oxidation of methyl dihydro-II-polyporenate A *a* : *b*-diacetate gave the corresponding methyl dihydro-II-*c* : *d*-diketopolyporenate A *a* : *b*-diacetate, which again absorbed at 2730 Å. The use of milder conditions resulted in the introduction of only one keto-group, giving methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate. The ultra-violet spectrum had a peak at 2510 Å, characteristic of an αββ-trisubstituted αβ-unsaturated ketone, and was similar to that of 8-ketolanost-9-en-2-yl acetate (IV) (Birchenough and McGhie, *J.*, 1950, 1249; Barton, Fawcett, and Thomas, *loc. cit.*). The infra-red spectrum of the monoketo-oxidation product, determined in Nujol, showed a strong band at 1658 cm.$^{-1}$, indicative of an αβ-unsaturated carbonyl group on a six-membered ring. In addition to the monoketone, a conjugated dienone containing only one acetoxyl group was obtained as a by-product. Its nature is discussed later.

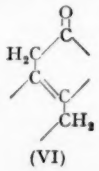
When methyl *a* : *b*-diketopolyporenate A was oxidised with chromic acid in acetic acid two further keto-groups were again introduced giving methyl *a* : *b* : *c* : *d*-tetraketopolyporenate A and the reactive double bond was again unattacked. The position of the ultra-violet absorption maximum (2830 Å) differed from that observed with methyl *c* : *d*-diketopolyporenate A *a* : *b*-diacetate and the corresponding dihydro-II-derivative. Absorption at about this wave-length has been observed with 8 : 11 : 12-triketolanosta-6 : 9-dien-2-yl acetate (V) by Dorée, McGhie, and Kurzer (*J.*, 1949, 570) ($\lambda_{max.}$, 2800 Å) and byVoser, Montavon, Gunthard, Jeger, and Ruzicka (*loc. cit.*) ($\lambda_{max.}$, 2850 Å). It is probable therefore that one of the keto-groups in methyl *a* : *b*-diketopolyporenate A is in the α-position to one of the methylene groups undergoing oxidation, *i.e.*, in the β-position to the unreactive double bond. Methyl *a* : *b*-diketopolyporenate A would then possess partial structure (VI) and the tetraketone oxidation product would be represented by (VII), the chromophoric system being very similar to that present in (V). The presence of an α-diketone grouping in the tetraketone was confirmed by oxidation with alkaline hydrogen peroxide whereupon the monomethyl ester of a tricarboxylic acid was formed without loss of carbon atoms. This result further proves that the α-diketone system is present in a ring.

Oxidation of methyl *b*-ketopolyporenate A *a*-acetate with chromic acid in acetic acid gave a triketone monoacetate, methyl *b* : *c* : *d*-triketopolyporenate A *a*-acetate, which also

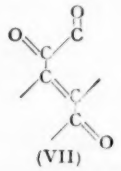
showed absorption at 2830 Å, indicative of the chromophore (VII). The presence of a cyclic α-diketone grouping was again demonstrated by oxidation with alkaline hydrogen peroxide. These results prove that the *b*-keto-group of the original keto-acetate is in the



(V)

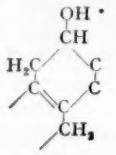


(VI)

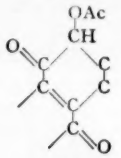


(VII)

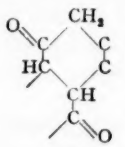
β-position to the unreactive double bond, and hence that in polyporenic acid the *b*-(*i.e.*, unreactive) hydroxyl group is similarly situated (cf. VIII). Confirmation of the partial structure (VIII) was provided by the zinc–acetic acid reduction of methyl dihydro-II-*c* : *d*-diketopolyporenate A *a* : *b*-diacetate which should contain the grouping (IX) if (VIII) is a correct partial structure for polyporenic acid A.



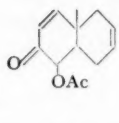
(VIII)



(IX)



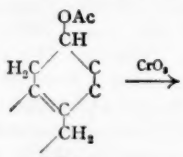
(X)



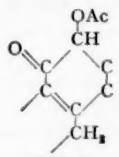
(XI)

The similar unsaturated diketone system in 8 : 11-diketolanostenyl acetate (III) is reduced by zinc and acetic acid to the saturated 1 : 4-diketone (Dorée, McGhie, and Kurzer, *J.*, 1948, 988). Further examples are known in which the acetoxyl group is eliminated from α-acetoxy-ketones by the action of zinc, *e.g.*, in (XI) (Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223). Therefore, if partial structure (IX) is present in methyl dihydro-II-*c* : *d*-diketopolyporenate A *a* : *b*-diacetate, reduction with zinc and acetic acid should lead to methyl *b*-deoxytetrahydro-II-*c* : *d*-diketopolyporenate A *a*-acetate, containing the grouping (X). The reduction product was indeed the methyl ester of a saturated monoacetoxy-diketo-acid. The infra-red spectrum of this compound, determined in carbon tetrachloride, showed strong bands at 1708 cm.$^{-1}$ and 1738 cm.$^{-1}$. The first band is due to the unconjugated keto-groups and the second to the ester groups.

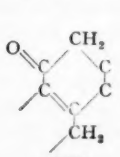
Reduction of the partial oxidation product, methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate, with zinc and acetic acid led to the replacement of the *b*-acetoxyl group by hydrogen giving methyl *b*-deoxydihydro-II-*c*-ketopolyporenate A *a*-acetate, showing an absorption maximum at 2540 Å. At first it was thought that these results implied that the introduction of the first keto-group (group *c*) had taken place between the double bond and the acetoxyl group, giving an α-acetoxy-ketone, the reactions being represented by the partial structures (XIII) and (XIV). However, this view was rendered untenable



(XII)



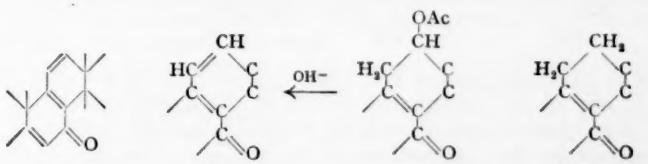
(XIII)



(XIV)

by the discovery that very mild alkali treatment of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate gave a conjugated dienone still containing one acetoxyl group, one carbomethoxyl group, and no hydroxyl group (infra-red spectrum). The absorption maximum at 3180 Å is indicative of the conjugation of the carbonyl group with the two double bonds in the *same* ring.

Although it is well known that a homoannular diene absorbs at a longer wave-length than the correspondingly substituted heteroannular diene, there is apparently no reference to a similar bathochromic shift in conjugated dienones possessing a homoannular diene system. Thus Fieser and Fieser (" Natural Products related to Phenanthrene," 3rd Edn., 1949, Reinhold Publ. Corp., p. 192) imply that no such shift occurs since their calculated maximum of 3180 Å for a $\Delta^{8(14),9(11)}$-dien-15-one in the steroid series makes no allowance for the homoannular bathochromic shift. The absorption maximum of cholesta-2 : 4-dien-6-one was found some years ago by the senior author (cf., Ross, *J.*, 1946, 735) to lie at 3160 Å (see also Reich, Walker, and Collins, *J. Org. Chem.*, 1951, **16**, 1753, who give 3140 Å). The latter, probably more accurate figure corresponds to a bathochromic shift of 360 Å comparable with that of *ca.* 410 Å in the homoannular diene series. In the tetracyclic triterpene group a cross-conjugated trienone (8-ketolanosta-6 : 9 : 11-trien-2-yl acetate) containing the chromophore (XV) has been described by Birchenough and McGhie (*J.*, *loc. cit.*). This compound shows maxima at 2560 and 3270 Å; the latter, due to the dienone system, again indicates a pronounced bathochromic shift.



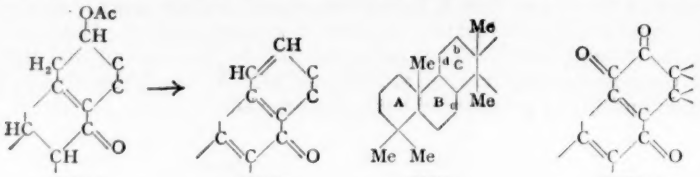
(XV) (XVI) (XVII) (XVIII)

The conjugated dienone resulting from the alkali treatment described above is formulated as (XVI). By using the value of 360 Å for the bathochromic shift due to the homoannular diene, the calculated absorption maximum for (XVI) is 3210 Å which agrees well with the observed figure of 3180 Å. The ready formation of the dienone indicates that the introduction of the first keto-group into methyl dihydro-II-polyporenate A *a* : *b*-diacetate occurs at the α-methylene group on the opposite side of the double bond from the *b*-acetoxyl group, the product being an αβ-unsaturated δ-acetoxy-ketone (XVII). This, on alkali treatment, is readily converted into the dienone (XVI).

With the partial formulation of methyl dihydro-II-*c*-ketopolyporenate *a* : *b*-diacetate as (XVII) it became clear that its reduction by zinc dust in acetic acid was not a simple reaction. In fact it takes place in two steps. The first is the elimination of acetic acid from the keto-diacetate with boiling acetic acid. This reaction occurs in the absence of zinc and the resultant conjugated dienone is identical with that obtained by alkali treatment and also with that described earlier as a by-product in the preparation of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate. In the latter case the dienone must arise from the monoketone as in the acetic acid reaction described above. The second step is the reduction of the γδ-double bond of the dienone, and this has been carried out independently. The product of this reaction (methyl *b*-deoxydihydro-II-*c*-ketopolyporenate A *a*-acetate; partial structure XVIII) is not identical with methyl acetyldihydromonoketoeburicoate (personal communication from Professor A. Robertson) and methyl acetylmonoketoelemenolate (Ruzicka, Rey, Spillman, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1695). Oxidation of the above *b*-deoxy-compound with chromic acid in acetic acid gave methyl *b*-deoxydihydro-II-*c* : *d*-diketopolyporenate A *a*-acetate, not identical with either methyl acetyldihydrodiketoeburicoate (Lahey and Strasser, *J.*, 1951, 873) or methyl acetyldiketoelemenolate (Ruzicka, Rey, Spillman, Baumgartner, *loc. cit.*).

The acid- and alkali-catalysed dehydrations described above have a ready parallel in Greenhalgh, Henbest, and Jones's finding (*J.*, 1952, 2375) that the αβ-unsaturated δ-hydroxy-ketone, 7α-hydroxycholest-4-en-3-one, undergoes dehydration very readily in the presence of mild acidic and alkaline reagents to the conjugated dienone, cholesta-4 : 6-dien-3-one. The ease of dehydration in the present case suggests that the *b*-hydroxyl group is polar.

Oxidation of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate with selenium dioxide in acetic acid gave a trienone containing only one acetoxyl group, and showing absorption maxima at 2600 and 3270 Å. These values correspond to the chromophore (XV) found in 8-ketolanosta-6 : 9 : 11-trien-2-yl acetate and indicate that the reaction (XIX) ⟶ (XX) has occurred. The very close similarity of the carbon skeleton of the partial structure (XIX) to that of lanosterol (I) suggests that the grouping (XXI) may be present in polyporenic acid A. In support of this partial formulation is the isolation of 1 : 2 : 8-trimethylphenanthrene from the products of the dehydrogenation of polyporenic acid A with selenium. Further oxidation of the trienone gave an impure product, the absorption spectrum of which indicated the presence of the partial structure (XXII). The absence of



(XIX) (XX) (XXI) (XXII)

any evidence of oxidation beyond this stage suggests that no hydrogen atoms occur at positions α to any of the unsaturated centres of the grouping (XXII). If the partial formulation of polyporenic acid A as (XXI) is correct, then the position of the *b*-hydroxyl group corresponds to the $C_{(12)}$-position in the steroids. The lack of reactivity of the *b*-keto-group compared with that of the 12-keto-group of the steroids is worthy of comment. (For a discussion of the reactivity of the 12-keto-group of the steroids see Fieser and Fieser, *op. cit.*, p. 124.) The lack of reactivity is almost certainly due to the presence of the additional methyl group at the position corresponding to $C_{(14)}$ in the steroids.

No conclusive evidence has yet been obtained about the position of the *a*-hydroxyl group. Dehydration experiments at present in progress suggest however that it is on the carbon atom adjacent to a *gem*-dimethyl group on ring A.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. Light petroleum refers to the fraction with b. p. 40—60° unless otherwise stated. The alumina used for chromatography had an activity of I—II. The derivatives of polyporenic acid A used as starting materials were prepared according to the methods described in the preceding two papers.

Methyl c : d-*Diketopolyporenate A* a : b-*Diacetate*.—Methyl polyporenate A *a* : *b*-diacetate (1·7 g.) was oxidised in acetic acid (70 c.c.) with chromic acid (3 g.) at 80—90°. After 90 minutes, dilution with water and isolation with ether yielded an oil (1·0 g.). This in ether was purified by chromatography on alumina (100 g.) to give an oily solid, crystallisation of which from methanol gave *methyl* c : d-*diketopolyporenate A* a : b-*diacetate* as pale yellow needles (0·5 g.), m. p. 141—142°, $[\alpha]_D^{20}$ +40·5° (*c*, 0·60) (Found : C, 70·4; H, 8·75. $C_{35}H_{50}O_8$ requires C, 70·3; H, 8·4%). Light absorption in ethanol : Max., 2730 Å; ε = 9500.

Methyl Dihydro-II-c : d-*dihetopolyporenate A* a : b-*Diacetate*.—Methyl dihydro-II-polyporenate A *a* : *b*-diacetate (1·5 g.) was oxidised in acetic acid (70 c.c) with chromic acid (2·4 g.) at 80—90°. After 50 minutes, dilution with water and isolation with ether yielded an oil (0·65 g.) which was adsorbed from benzene (20 c.c.) on alumina (100 g.). Elution with benzene–ether (4 : 1; 400 c.c.) gave an oil (60 m.g.), which crystallised in contact with methanol. Recrystallisation from the same solvent gave *methyl dihydro*-II-b : c : d-*triketopolyporenate A* a-*acetate* as yellow prisms, m. p. 150—151·5° (Found : C, 71·7; H, 9·0. $C_{33}H_{48}O_7$ requires C, 71·2; H, 8·7%). Light absorption in ethanol : Max., 2840 Å; ε = 8150. Further elution with benzene–ether (7 : 3; 500 c.c.) gave a fraction (0·5 g.) which formed pale yellow needles (from methanol) of *methyl dihydro-II*-c : d-*diketopolyporenate A* a : b-*diacetate* (0·45 g.), m. p. 148—149·5°, $[\alpha]_D^{20}$ +176° (*c*, 0·15) (Found : C, 69·9; H, 8·95. $C_{35}H_{52}O_8$ requires C, 69·95, H, 8·7%). Light absorption in ethanol : Max., 2730 Å; ε = 9500.

Methyl Dihydro-II-c-*hetopolyporenate A* a : b-*Diacetate*.—Methyl dihydro-II-polyporenate A *a* : *b*-diacetate (2 g.) was oxidised in acetic acid (100 c.c.) with chromic acid (0·9 g.) at 80—90°.

After 10 minutes, dilution with water and isolation with ether yielded an oil (1·95 g.). This was dissolved in benzene–ether (7 : 3; 500 c.c.); chromatography on alumina (100 g.) gave a solid, several recrystallisations of which from methanol gave *methyl dihydro-II-*c*-ketopolyporenate A* a : b-*diacetate* as prisms (1·3 g.), m. p. 172—174°, $[\alpha]_D^{20}$ +60° (*c*, 0·94) (Found: C, 71·85; H, 9·5. $C_{35}H_{52}O_7$ requires C, 71·6; H, 9·2%). Light absorption in ethanol; Max., 2510 Å; $\varepsilon = 10{,}000$. In a second preparation on the same scale the reaction mixture was allowed to cool to room temperature before dilution with water. The oil (1·97 g.) isolated with ether was adsorbed from benzene (50 c.c.) on alumina (200 g.). Elution with benzene–ether (9 : 1; 300 c.c.) gave a fraction (0·4 g.), several recrystallisations of which from methanol gave the *dienone* (XVI) as prisms, m. p. 194—195°, $[\alpha]_D^{20}$ −27° (*c*, 0·61) (Found: C, 75·45; H, 9·8. $C_{33}H_{50}O_5$ requires C, 75·25; H, 9·6%). Light absorption in ethanol: Max., 3180 Å; $\varepsilon = 7600$. Further elution with benzene–ether (7 : 3; 800 c.c.) yielded a fraction (1·5 g.) which gave the monoketo-diacetate, described above, as prisms (from methanol), m. p. 172—174°, $[\alpha]_D^{20}$ +60° (*c*, 0·85).

Methyl a : b : c : d-*Tetraketopolyporenate A*.—Methyl *a* : *b*-diketopolyporenate A (1·5 g.) was oxidised in acetic acid (70 c.c.) with chromic acid (2·4 g.) at 80—90°. After 30 minutes, dilution with water and isolation with ether yielded an oily solid (0·55 g.). This was dissolved in benzene (20 c.c.); chromatography on alumina (60 g.) and crystallisation from methanol gave *methyl* a : b : c : d-*tetraketopolyporenate A* as bright orange plates (0·4 g.), m. p. 141—142°, $[\alpha]_D^{20}$ +34° (*c*, 0·8) (Found: C, 73·3; H, 8·5. $C_{31}H_{42}O_6$ requires C, 72·9; H, 8·1%). Light absorption in ethanol: Max., 2830 Å; $\varepsilon = 9000$.

Action of Alkaline Hydrogen Peroxide on Methyl a : b : c : d-*Tetraketopolyporenate*.—The tetraketone (170 mg.) was dissolved in dioxan (20 c.c.), and methanolic potassium hydroxide (10%; 8 c.c.) and hydrogen peroxide (100-vol.; 4 c.c.) were added. After 10 minutes at 50° the yellow colour of the reaction mixture had almost disappeared. More hydrogen peroxide (1 c.c.) was added and then, after 10 minutes at 20°, the solution was poured into water. The product, isolated with ether, was divided into a neutral and an acidic fraction. The neutral *ester* (40 mg.) crystallised from methanol as needles, m. p. 173·5—174·5°, $[\alpha]_D^{20}$ +59·5° (*c*, 0·78) (Found: C, 74·5; H, 9·4. $C_{31}H_{48}O_5$ requires C, 74·7; H, 9·25%). Light absorption in ethanol: Max., 2410 Å; $\varepsilon = 9200$. The acidic fraction gave a tricarboxylic acid monomethyl ester as a colourless glass (120 m.g.), $[\alpha]_D^{20}$ −22·5° (*c*, 1·77). Light absorption in ethanol: Max., 2390—2400 Å; $\varepsilon = 8300$. The glass was dissolved in acetone (5 c.c.), treated with an excess of diazomethane in ether, and kept at 20° for 30 minutes. After decomposition of the excess of diazomethane the *trimethyl* ester was isolated as a colourless, uncrystallisable amorphous solid (100 mg.), $[\alpha]_D^{20}$ −23° (*c*, 0·55) (Found: C, 68·85; H, 8·8. $C_{33}H_{48}O_8$ requires C, 69·2; H, 8·45%). Light absorption in ethanol; Max., 2360—2380 Å; $\varepsilon = 8500$.

Methyl b : c : d-*Triketopolyporenate A* a-*Acetate*.—Methyl *b*-ketopolyporenate A *a*-acetate (1·4 g.) was oxidised in acetic acid (70 c.c.) with chromic acid (2·14 g.) at 80—90°. After 10 minutes, dilution with water and isolation with ether yielded a neutral fraction, which gave *methyl* b : c : d-*triketopolyporenate A* a-*acetate* as bright orange needles (0·6 g.) (from methanol), m. p. 158—159°, $[\alpha]_D^{20}$ −103° (*c*, 1·0) (Found: C, 71·5; H, 8·7. $C_{35}H_{46}O_7$ requires C, 71·5; H, 8·4%). Light absorption in ethanol: Max., 2840 Å; $\varepsilon = 9250$.

Action of Alkaline Hydrogen Peroxide on Methyl b : c : d-*Triketopolyporenate A* a-*Acetate*.—Methyl *b* : *c* : *d*-triketopolyporenate A *a*-acetate (1·14 g.) was dissolved in dioxan (60 c.c.), and methanolic potassium hydroxide (10%; 40 c.c.) and hydrogen peroxide (100-vol.; 15 c.c.) were added. After 10 minutes at 50° more hydrogen peroxide (10 c.c.) was added and the mixture was kept at 20° for 10 minutes, by which time the yellow colour had almost disappeared. Dilution with water and extraction with ether yielded a neutral glass (0·03 g.) which was not investigated further. Acidification of the extracted alkaline solution and isolation with ether yielded a tricarboxylic acid monomethyl ester as a colourless glass (1·0 g.), $[\alpha]_D^{20}$ −37° (*c*, 1·0). Light absorption in ethanol: Max., 2360—2380 Å; $\varepsilon = 8500$. The glass (0·89 g.) was dissolved in acetone (5 c.c.), treated with an excess of diazomethane in ether, and kept at 20° for 30 minutes. After decomposition of the excess of diazomethane the *trimethyl* ester was isolated as an amorphous solid (0·88 g.). This was dissolved in ether (5 c.c.) and chromatographed on alumina (60 g.), but only an uncrystallisable gum was obtained, having $[\alpha]_D^{20}$ −37·5° (*c*, 1·23) (Found: C, 67·7; H, 8·2. $C_{35}H_{52}O_9$ requires C, 68·1; H, 8·5%).

*Zinc Dust Reduction of Methyl Dihydro-II-*c : d-*Diketopolyporenate A* a : b-*Diacetate*.—To a boiling solution of methyl dihydro-II-*c* : *d*-diketopolyporenate A *a* : *b*-diacetate (80 mg.) in acetic acid (10 c.c.), zinc dust (500 mg.) was added in small portions during 45 minutes; the solution became colourless on the first addition. After cooling, the solution was filtered into water, extraction of which with ether led to the isolation of a crystalline neutral fraction (75 mg.).

Several recrystallisations of this from methanol gave *methyl* b-*deoxytetrahydro*-II-c : d-*diketopolyporenate A* a-*acetate* as plates, m. p. 164—165°, $[\alpha]_D^{20}$ +39·5° (*c*, 0·34) (Found : C, 73·05; H, 9·85. $C_{35}H_{52}O_6$ requires C, 72·75; H, 9·6%). Light absorption in ethanol : 2730 (ε = 5) and 2100 Å (ε = 490).

Zinc Dust Reduction of Methyl Dihydro-II-c-ketopolyporenate A a : b-*Diacetate*.—To a boiling solution of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate (400 mg.) in acetic acid (20 c.c.), zinc dust (1·5 g.) was added in small portions during 1 hour. The cooled solution was filtered into water, extraction of which with ether led to the isolation of a solid neutral fraction (360 mg.) which was adsorbed from benzene (20 c.c.) on alumina (100 g.). Elution with benzene–ether (19 : 1; 600 c.c.) gave a fraction, crystallisation of which from methanol–chloroform gave *methyl 6-deoxydihydro-II-c-ketopolyporenate A* a-*acetate* as long needles, m. p. 210—212·5°, $[\alpha]_D^{20}$ −67·5° (*c*, 0·48) (Found : C, 75·35; H, 10·05. $C_{33}H_{52}O_5$ requires C, 75·05; H, 9·9%). Light absorption in ethanol : Max., 2540 Å; ε = 10,000.

Alkali Treatment of Methyl Dihydro-II-c-ketopolyporenate A a : b-*Diacetate*.—Methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate (230 mg.) was refluxed with methanolic potassium hydroxide (20 c.c.; 1%) for 30 minutes. After dilution with water the neutral and the acidic products were separated. The yield of the latter was negligible, but the former (200 mg.), after several recrystallisations from methanol, gave (XVI) as prisms, m. p. 192—193° undepressed when the dienone was mixed with that obtained in the preparation of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate, $[\alpha]_D^{20}$ −31° (*c*, 0·53) (Found : C, 75·0; H, 9·6. Calc. for $C_{33}H_{50}O_5$: C, 75·25; H, 9·6%). Light absorption in ethanol : Max., 3180 Å; ε = 7500.

Action of Boiling Acetic Acid on Methyl Dihydro-II-c-ketopolyporenate A a : b-*Diacetate*.—Methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate (275 mg.) was refluxed with acetic acid (20 c.c.) for 2 hours. The acetic acid was then evaporated under reduced pressure, leaving an oily solid. Two recrystallisations from methanol gave (XVI) as prisms, m. p. and mixed m. p. 192—194°, $[\alpha]_D^{20}$ −30° (*c*, 0·65). Light absorption in ethanol : Max., 3180 Å; ε = 6650.

Reduction of the Dienone (XVI) *with Zinc Dust in Acetic Acid*.—To a boiling solution of (XVI) (115 mg.) in acetic acid (15 c.c.), zinc dust (2 g.) was added in small portions during 1 hour. The cooled solution was filtered into water, and extraction with ether led to the isolation of a solid neutral fraction (100 mg.). Several recrystallisations from chloroform–methanol gave methyl *b*-deoxydihydro-II-*c*-ketopolyporenate A *a*-acetate as needles, m. p. 209—210°, $[\alpha]_D^{20}$ −66° (*c*, 0·66). Light absorption in ethanol : Max., 2540 Å; ε = 8950. The infra-red spectrum was identical with that of a specimen prepared by zinc dust reduction of methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate in acetic acid.

Oxidation of Methyl Dihydro-II-c-ketopolyporenate A a : b-*Diacetate with Selenium Dioxide*.—Methyl dihydro-II-*c*-ketopolyporenate A *a* : *b*-diacetate (320 mg.) in acetic acid (100 c.c.) was refluxed with selenium dioxide (200 mg.) for 3 hours. The selenium was filtered off and the solution poured into water. The neutral product was then isolated as an oil (300 mg.), chromatographed in ether on alumina (30 g.), and crystallised from methanol, giving the *trienone* (XX) (260 mg.) as plates, m. p. 171—174°, $[\alpha]_D^{20}$ +29° (*c*, 0·52) (Found : C, 75·2; H, 9·25. $C_{33}H_{48}O_5$ requires C, 75·5; H, 9·2%). Light absorption in ethanol : Max., 2600 (ε = 9600) and 3270 Å (ε = 9600).

Dehydrogenation of Polyporenic Acid A with Selenium.—Polyporenic acid A (20 g.) was heated at 220—230° (bath-temp.) in nitrogen until decarboxylation was complete. Precipitated selenium (10 g.) was then added and the bath-temperature raised to 320°. Selenium (5 g.) was added at hourly intervals until a total quantity of 30 g. had been used. The heating was continued for a further 30 hours, and then the product was cooled, powdered, and extracted with ether and benzene. The extract was dried (Na_2SO_4) and evaporated, giving a dark brown oil (14 g.). This was distilled under reduced pressure (2 mm.) to give the following fractions : (i) colourless mobile liquid (0·4 g.), b. p. 40—60° (bath-temp.); (ii) pale brown viscous oil (1·1 g.), b. p. 170—230° (bath-temp.); residue—a dark brown oily solid (12 g.).

Fraction (ii) was chromatographed on alumina (100 g.), and the solid fractions obtained by elution with light petroleum–benzene (9·1) gave 1 : 2 : 8-trimethylphenanthrene (0·6 g.) as plates, m. p. 145—146°, after many recrystallisations from ethanol (Found : C, 92·2; H, 7·0. Calc. for $C_{17}H_{16}$: C, 92·7; H, 7·3%). The picrate and the *s*-trinitrobenzene adduct had m. p.s 163—164° and 190—191°, respectively. No depressions in m. p. were observed when these three compounds were admixed with corresponding authentic samples. The absorption spectrum of the hydrocarbon, $\lambda_{max.}$ 2630, 2840, 2950, 3080, 3400, and 3560 Å ($\varepsilon_{max.}$ 58,900, 13,200, 11,700, 14,100, 350, and 170 respectively), was also characteristic of 1 : 2 : 8-trimethylphenanthrene.

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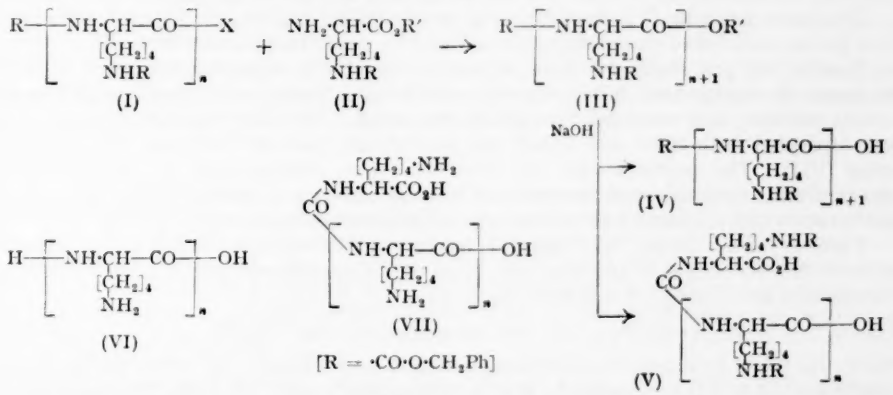
95. *Some Peptides of Lysine.*

By S. G. WALEY and J. WATSON.

Syntheses of di-, tri-, tetra-, and penta-lysine * (VI; $n = 2$, 3, 4, and 5) have been achieved, mainly by Wieland and Sehring's method (*Annalen*, 1950, **569**, 122). Difficulties were encountered in the separation of ureas (V) formed as by-products in the hydrolysis of the carbobenzyloxypeptide esters. Separation of these peptides of lysine by paper chromatography and their subsequent estimation by the ninhydrin colour reaction have been studied. The titration curves of the peptides are also described.

ENZYMIC hydrolysis of polylysine gives dilysine * (VI; $n = 2$) and trilysine (VI; $n = 3$) as final products. Higher peptides are also formed during the reaction (Waley and Watson, unpublished work). To aid identification of these substances, their synthesis was undertaken and some of their properties were studied.

The syntheses were of the type shown in the scheme. Since both the terminal α- and the ε-amino-groups in (III) are protected by the same group the α-amino-group cannot be preferentially liberated and thus the peptide chain can only be built up by the addition of monomeric units. As well as the older methods using acid chlorides (restricted to the synthesis of dipeptides) and azides (Fruton, *Adv. Protein Chem.*, 1949, **5**, 1), there are many recent methods (Wieland, *Angew. Chemie*, 1951, **63**, 7) employing different acylating agents. We have used the mixed anhydrides with benzoic acid (Wieland and Sehring, *Annalen*, 1950, **569**, 122) extensively in our work.



For the preparation of dilysine, *NN'*-dicarbobenzyloxylysine chloride (I; $n = 1$, X = Cl) (Bergmann, Zervas, and Ross, *J. Biol. Chem.*, 1935, **111**, 245) was washed with ice-water (cf. Synge, *Biochem. J.*, 1948, **42**, 99) and coupled with N^{ϵ}-carbobenzyloxylysine methyl ester (II; R' = Me), and the dipeptide ester (III; $n = 1$, R' = Me) hydrolysed with alkali to the acid (IV; $n = 1$). Hydrogenation over palladised charcoal gave dilysine (VI; $n = 2$), characterised as the Reineckate and flavianate. The ester (III; $n = 1$, R' = Me) was also prepared in rather better yield from the mixed anhydride (I; $n = 1$, X = O·COPh). The preparation of dilysine from Fischer and Susuki's "lysine anhydride" (*Ber.*, 1905, **38**, 4173) has been reported by Greenstein (*J. Biol. Chem.*, 1933,

* Since L-lysine was used throughout this work, the designation of the optical form is omitted; also, lysyl-lysine is written as dilysine, and the higher peptides are similarly described.

101, 603), but it has since been shown by Adamson (*J.*, 1943, 39) that the product obtained by Fischer and Susuki from lysine methyl ester is a mixture.

For the next stage the dipeptide hydrazide (I; $n = 2$, X = $NH{\cdot}NH_2$) was converted into the azide and condensed with (II; R′ = Me) to give the tripeptide ester (III; $n = 2$, R′ = Me). Alkaline hydrolysis gave material containing the urea (V; $n = 2$). The urea was separated by its greater solubility in weakly alkaline solutions; the purified acid (IV; $n = 2$) was then reduced to trilysine (VI; $n = 3$). The formation of ureas by the action of alkali on carbalkyloxy-peptides was first observed by Fischer (*Ber.*, 1902, **35**, 1095), correctly interpreted by Wessely and Kemm (*Z. physiol. Chem.*, 1928, **174**, 306; cf. Goldschmidt and Wick, *Annalen*, 1952, **575**, 217), and used as a degradative method by Wessely, Schlögl, and Korger (*Nature*, 1952, **169**, 708). To avoid urea formation, the benzyl ester (II; R′ = CH_2Ph) was used in the Wieland synthesis to prepare the tripeptide benzyl ester (III; $n = 2$, R′ = CH_2Ph), which on reduction gave trilysine. The use of benzyl esters was not necessary in the preparation of dilysine, since urea formation was not observed in this case. After these peptides had been synthesised Brand and his co-workers (*J. Amer. Chem. Soc.*, 1951, **73**, 4025, 4027) described their preparation by the azide method.

For the synthesis of tetralysine, the tripeptide acid (IV; $n = 2$) is required, and this can only be prepared by saponification of the ester. After separation from the urea, the acid (IV; $n = 2$) was converted into the mixed anhydride of benzoic acid and coupled with the amino-ester (II; R′ = CH_2Ph) to give the tetrapeptide benzyl ester (III; $n = 3$, R′ = CH_2Ph). Hydrogenation gave tetralysine (VI; $n = 4$). The tetrapeptide methyl ester (III; $n = 3$, R′ = Me), required for the synthesis of pentalysine, was prepared in the same way as the benzyl ester. Saponification gave the acid (IV; $n = 3$) contaminated with material of lower equivalent weight. The contaminant, probably the urea (V; $n = 3$), has not been obtained pure. The acid (IV; $n = 3$) was converted by the Wieland method into the pentapeptide benzyl ester (III; $n = 4$, R′ = CH_2Ph), and thence into pentalysine (VI; $n = 5$).

Of the methods used above for lengthening the peptide chain, the Wieland synthesis is preferred to the azide method as it is easier and gives purer products.

The lysine peptides (VI) were obtained as crystalline hygroscopic hydrochlorides and their purity established chromatographically and by potentiometric titration.

None of the previously described solvents satisfactorily separated the lysine peptides on paper chromatograms, but a mixture of *n*-butanol, acetic acid, pyridine, and water proved suitable, and was used throughout this work. The four peptides of lysine were well separated both from each other and from lysine, but not from the corresponding ureas (VII). The peptides and the ureas were best distinguished by potentiometric titration, since only the peptides possessed a group buffering at pH 7—8, and the shape of the titration curve showed whether the peptide was contaminated with the urea.

Pardee (*J. Biol. Chem.*, 1951, **190**, 757) has shown that a simple relation can be deduced between the R_F values of peptides and those of the constituent amino-acids. When all the residues are of one kind this takes the form

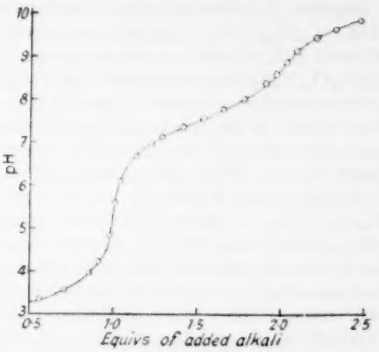
$$\ln(1/R_F - 1) - n\ln(1/R_F' - 1) = [(n-1)A + B]/RT$$

where R_F refers to a peptide containing n amino-acid residues, R_F' refers to the parent amino-acid, A and B are constants, R is the gas constant, and T the absolute temperature. This equation holds accurately for peptides di- to hepta-lysine; the R_F values for hexa- and hepta-lysine were obtained from chromatograms of an acid hydrolysate of polylysine. The constants A and B were −450 cal./mole and 0 respectively, which are comparable with the values found in other solvents by Pardee. The constant B represents the difference between the work required to transfer the terminal groups of the peptide and those of the amino-acid from one phase to the other. Thus in our case this difference is negligible.

The estimation of these lysine peptides after separation by paper chromatography was also investigated. The method used, which depends on the ninhydrin colour reaction (Boissonnas, *Helv. Chim. Acta*, 1950, **33**, 1975; Fowden, *Biochem. J.*, 1951, **48**, 327) has hitherto only been applied to the estimation of amino-acids. We have successfully estimated di- and tri-lysine following Fowden's procedure with only minor modifications.

Although the optical density was a linear function of the amount of peptide present, the gradient differed in different chromatograms so that calibration solutions had to be run each time.

The titration curves of the peptides were determined at 25·8° in a solution 0·083M with respect to potassium chloride, a glass electrode being used; a typical curve is shown in the Figure. End points at *ca.* pH 5·5 and pH 8·5, and buffering at *ca.* pH 7·5 are clearly discernible; the last is due to the α-amino-group. The amount of titrant consumed between the end-points is a measure of the amount of α-amino-nitrogen, which may be compared with the total amount of nitrogen found by analysis. Another measure of the amount of α-amino-nitrogen is provided by the gradient of the curve where buffering is a maximum, since it may readily be shown that, when the buffering power of the solvent is negligible, the concentration of the buffering group is $1{\cdot}737\beta$, where β is the buffer capacity.



Titration of dilysine, $4{\cdot}77 \times 10^{-3}$M. *Theoretical line calc. with* $pK_1 = 3{\cdot}1$, $pK_2 = 7{\cdot}56$, $pK_3 = 10{\cdot}35$, *and* $pK_4 = 10{\cdot}85$.

The agreement between both these measures of the α-amino-nitrogen and that calculated from the total nitrogen was satisfactory in all cases. The titration curve of the urea (VII; $n = 2$), however, showed no buffering between pH 5 and pH 9. The pK's of the α-amino-groups are given in the Table. There appears to be a linear relation between pK and the reciprocal of the number of lysine residues in the peptide.

Peptide	Dilysine	Trilysine	Tetralysine	Pentalysine
pK of α-NH_2-group	7·56	7·26	7·15	7·07

Experimental

Dicarbobenzyloxylysine (I; $n = 1$, X = OH) and ε-carbobenzyloxylysine methyl ester hydrochloride (II; R′ = Me) were prepared by the method of Bergmann, Zervas, and Ross (*loc. cit.*); paper chromatography showed the latter to be contaminated with lysine methyl ester hydrochloride. Before use, the ε-carbobenzyloxylysine methyl ester hydrochloride was decomposed with aqueous potassium hydrogen carbonate and extracted with ethyl acetate; the lysine methyl ester remained in the aqueous layer. A similar procedure was applied to ε-carbobenzyloxylysine benzyl ester hydrochloride (II; R′ = CH_2Ph) (Erlanger and Brand, *J. Amer. Chem. Soc.*, 1951, **73**, 4025).

Tri-(N-carbobenzyloxy)dilysine Methyl Ester (III; $n = 1$, R′ = Me).—(*a*) Powdered phosphorus pentachloride (14 g.) was added to dicarbobenzyloxylysine (26 g.) in dry ether (300 c.c.) at 0°. After 2 hours, the filtered solution was shaken twice with ice-water, and added to ε-carbobenzyloxylysine methyl ester (18 g.) in ethyl acetate (450 c.c.) and 1·4N-potassium hydrogen carbonate (150 c.c.). The mixture was stirred for 2 hours, and the dipeptide ester (24·3 g., 56%; m. p. 121—122°) collected and washed with water and then ether. Recrystallisation from ethyl acetate raised the m. p. to 123° (Erlanger and Brand, *loc. cit.*, give m. p. 115—117°), $[\alpha]_D^{20}$ −8·1° (*c*, 4·45 in EtOH) (Found: C, 64·5; H, 6·7; N, 8·3. Calc. for $C_{37}H_{46}O_9N_4$: C, 64·4; H, 6·7; N, 8·1%).

(*b*) Benzoyl chloride (5·16 c.c.) was added to dicarbobenzyloxylysine (18·4 g.) and 1-ethylpiperidine (5·91 c.c.) in benzonitrile (50 c.c.) at 0°. After 10 minutes at room temperature this solution was added to ε-carbobenzyloxylysine methyl ester (13·06 g.) in ethyl acetate (200 c.c.), ether (200 c.c.), and 1·4N-potassium hydrogen carbonate (78 c.c.). The mixture was stirred

vigorously until much solid had separated and then shaken at intervals during 1 hour. The dipeptide ester (19 g., 62%; m. p. 121—123°) was collected and washed with water and ether.

Tri-(N-carbobenzyloxy)dilysine (IV; $n = 1$).—N-Sodium hydroxide (50 c.c.), tricarbobenzyloxydilysine methyl ester (26 g.), and acetone (250 c.c.) were shaken for 1 hour and neutralised with 2·47N-hydrochloric acid (20·25 c.c.), and the acetone was distilled off. The dipeptide (22 g., 86%; m. p. 145—147°) was collected; recrystallisation from ethyl acetate did not raise the m. p. (Erlanger and Brand, *loc. cit.* give m. p. 145°); $[\alpha]_D^{20}$ was −1·5° (*c*, 4·98 in AcOH) (Found: C, 63·8; H, 6·6; N, 8·3%; equiv., 682. Calc. for $C_{36}H_{44}O_9N_4$: C, 63·9; H, 6·5; N, 8·3%; equiv., 690).

Dilysine (VI; $n = 2$).—Tricarbobenzyloxydilysine (1·98 g.) in methanol (30 c.c.) and 0·98N-hydrochloric acid (6·0 c.c.) was reduced in hydrogen in the presence of 10% palladised charcoal (2 g.) for 2½ hours. The filtered mixture was evaporated, and the residue crystallised by trituration with methanol (yield 0·444 g.). It gave a negative biuret reaction and had R_F 0·17. *Dilysine di-Reineckate* crystallised from water in pink plates (Found: C, 25·0; H, 4·9; Cr, 10·9. $C_{20}H_{38}O_3N_{16}S_8Cr_2,3H_2O$ requires C, 24·9; H, 4·6; Cr, 10·8%). The *diflavianate* crystallised from 80% ethanol in yellow prisms, m. p. 209° (decomp.) (Found: C, 40·1; H, 4·4; S, 6·8. $C_{32}H_{38}O_{19}N_8S_2,3H_2O$ requires C, 40·2; H, 4·6; S, 6·7%).

Tri-(N-carbobenzyloxy)dilysine Hydrazide (I; $n = 2$, X = NH·NH_2).—Anhydrous hydrazine (15 c.c.) was added to tricarbobenzyloxydilysine methyl ester (30 g.) in methanol (175 c.c.). After several days the solid was collected, washed with water, and recrystallised from aqueous ethanol (yield 21·7 g., 72%; m. p. 186—187°). Further recrystallisation raised the m. p. to 190—191° (Erlanger and Brand, *loc. cit.* give m. p. 187°) (Found: C, 62·7; H, 6·85; N, 12·0. Calc. for $C_{36}H_{46}O_8N_6$: C, 62·6; H, 6·7; N, 12·2%).

Tetra-(N-carbobenzyloxy)trilysine Methyl Ester (III; $n = 2$, R′ = Me).—(*a*) Tricarbobenzyloxydilysine hydrazide was converted into the azide and condensed with ε-carbobenzyloxylysine methyl ester essentially as described by Erlanger and Brand. Their product, however, melted at 142—145°, ours at 160—162°; $[\alpha]_D^{20}$ was −10·4° (*c*, 5·0 in AcOH) (Found: C, 64·2; H, 7·1; N, 9·15. Calc. for $C_{51}H_{64}O_{12}N_6$: C, 64·3; H, 6·7; N, 8·8%).

(*b*) Tricarbobenzyloxydilysine (11·1 g.) in tetrahydrofuran (30 c.c.) and 1-ethylpiperidine (2·22 c.c.) was treated at 0° with benzoyl chloride (1·88 c.c.), and the mixture added to ε-carbobenzyloxylysine methyl ester (7·1 g.) in ethyl acetate (90 c.c.) and 1·4N-potassium hydrogen carbonate (30 c.c.). After 45 minutes' vigorous stirring at 0° the product was collected and recrystallised from methanol (yield 9·1 g., 58%; m. p. 164—165·5°) (Found: C, 63·6; H, 6·9; N, 9·4. Calc. for $C_{51}H_{64}O_{12}N_6$: C, 64·3; H, 6·7; N, 8·8%). The condensation can also be carried out in benzonitrile but the product is less pure.

Tetra-(N-carbobenzyloxy)trilysine Benzyl Ester (III; $n = 2$, R′ = CH_2Ph).—Tricarbobenzyloxydilysine was converted into the mixed anhydride and condensed with ε-carbobenzyloxylysine benzyl ester, as described for tricarbobenzyloxydilysine methyl ester. The product (50%) had m. p. 157—158° after recrystallisation from 95% ethanol. The analytical sample melted at 161—162° (Brand, Erlanger, Polatnick, Sachs, and Kirschenbaum, *J. Amer. Chem. Soc.*, 1951, **73**, 4026, give m. p. 153—154°) (Found: C, 66·6; H, 6·9; N, 8·4. Calc. for $C_{57}H_{68}O_{12}N_6$: C, 66·6; H, 6·6; N, 8·2%).

Tetra-(N-carbobenzyloxy)trilysine (IV; $n = 2$).—Tetracarbobenzyloxytrilysine methyl ester (21·1 g.), suspended in acetone (150 c.c.) and 0·6N-sodium hydroxide (50 c.c.), was stirred for 1½ hours, then filtered, and the filtrate diluted with water (700 c.c.) and saturated with carbon dioxide. The gelatinous precipitate was collected (filtrate A), washed with water, dissolved in warm acetone (500 c.c.) and 3N-hydrochloric acid (10 c.c.), and filtered, and acetone removed from the filtrate by distillation. *Tetracarbobenzyloxytrilysine* was collected and recrystallised from ethyl methyl ketone–ether (charcoal) (yield, 10 g., 52%; m. p. 173—174°) (Found: C, 63·9; H, 6·4; N, 9·2%; equiv., 946, 966. $C_{50}H_{62}O_{12}N_6$ requires C, 64·0; H, 6·6; N, 9·0%; equiv., 939).

When the filtrate A was acidified the *urea* (V; $n = 2$) was precipitated; it was purified by extraction from ethyl acetate with 1·4N-potassium hydrogen carbonate and acidification. Recrystallisation from ethyl methyl ketone–ether gave a sample, m. p. 153—155° (decomp.) (0·74 g. of m. p. 150—152°) (Found: C, 60·8; H, 7·0; N, 9·8%; equiv., 441. $C_{43}H_{56}O_{12}N_6$ requires C, 60·9; H, 6·6; N, 9·9%; equiv., 424).

Trilysine (VI; $n = 3$).—Tetracarbobenzyloxytrilysine benzyl ester was reduced in the presence of palladised charcoal and the product isolated as described by Brand *et al.* (*loc. cit.*); it had R_F 0·12 and gave a negative biuret reaction.

$N^{\alpha'}$-(*Lysine*-$N^{\alpha''}$-*carbonyl*)*dilysine* (VII; $n = 2$).—The carbobenzyloxyurea (V; $n = 2$) (0·48 g.) in 85% acetic acid (20 c.c.) and 0·98N-hydrochloric acid (0·58 c.c.) was reduced in the

presence of 10% palladised charcoal (1 g.) for 2½ hours. After evaporation of the filtered solution, the product crystallised under methanol–ethanol; its R_F was 0·12.

Penta-(N-carbobenzyloxy)tetralysine Methyl Ester (III; $n = 3$, R′ = Me).—The *tetrapeptide methyl ester* was prepared in 62% yield from tetracarbobenzyloxytrilysine as described for tetracarbobenzyloxytrilysine methyl ester [method (*b*)]. After recrystallisation from methanol it melted at 156—157° (Found: C, 64·4; H, 6·9; N, 9·3. $C_{65}H_{82}O_{15}N_8$ requires C, 64·3; H, 6·8; N, 9·2%).

Penta-(N-carbobenzyloxy)tetralysine Benzyl Ester (III; $n = 3$, R′ = CH_2Ph), similarly prepared in 48% yield and recrystallised from 95% ethanol, had m. p. 170—172° (Found: C, 66·25; H, 7·1; N, 9·25. $C_{71}H_{86}O_{15}N_8$ requires C, 66·1; H, 6·7; N, 8·7%).

Penta-(N-carbobenzyloxy)tetralysine (IV; $n = 3$).—Pentacarbobenzyloxytetralysine methyl ester (3·3 g.) was suspended in hot acetone (50 c.c.) and 1·02N-sodium hydroxide (4 c.c.) and stirred for 30 minutes. The mixture was again warmed, treated with water (4 c.c.), warmed again after 20 minutes, and treated with 1·02N-sodium hydroxide (0·4 c.c.). After a further 20 minutes the mixture was diluted with water (100 c.c.) and acetone (60 c.c.) and saturated with carbon dioxide. The precipitate was dissolved in warm acetone (200 c.c.) and 3N-hydrochloric acid (1·1 c.c.), diluted with water, and freed from acetone by distillation. The *tetrapeptide*, recrystallised from ethyl methyl ketone (0·64 g. of m. p. 157—159°) had m. p. 162—163° (Found: C, 63·2; H, 7·0; N, 9·7%; equiv., 1204. $C_{64}H_{80}O_{15}N_8$ requires C, 64·0; H, 6·7; N, 9·3%; equiv. 1201).

Tetralysine (VI; $n = 4$).—Pentacarbobenzyloxytetralysine benzyl ester was reduced in the same way as tetracarbobenzyloxytrilysine benzyl ester; the tetralysine, precipitated from methanol by ethanol, had R_F 0·09 and gave a positive biuret reaction.

Hexa-(N-carbobenzyloxy)pentalysine Benzyl Ester (III; $n = 4$, R′ = CH_2Ph).—The viscous solution of pentacarbobenzyloxytetralysine (0·592 g.) in benzonitrile (4 c.c.) and 1-ethylpiperidine (0·055 g.) was stirred with benzoyl chloride (0·07 g.) for 15 minutes, and to it were added ε-carbobenzyloxylysine benzyl ester (0·21 g.) in ethyl acetate (6 c.c.) and 1·4N-potassium hydrogen carbonate (1·5 c.c.). After 2 hours' shaking, the *pentapeptide benzyl ester* was collected, washed with water and ether, and recrystallised thrice from ethanol (yield, 0·252 g. of m. p. 175—177°), m. p. 177—178° (Found: C, 65·5; H, 6·6; N, 9·5. $C_{85}H_{104}O_{18}N_{10}$ requires C, 65·8; H, 6·7; N, 9·0%).

Pentalysine (VI; $n = 5$).—The foregoing ester was reduced in the same way as tetracarbobenzyloxytrilysine benzyl ester; pentalysine was precipitated from methanol by ethanol–ether; it gave a positive biuret reaction and had R_F 0·06.

Paper Chromatography.—(a) *Qualitative.* The descending technique was used. The solvent was *n*-butanol–acetic acid–water–pyridine (30 : 6 : 24 : 20; homogeneous). Whatman No. 1 or No. 4 papers were employed. R_F values for the individual peptides given above are calculated on the basis of R_F for lysine = 0·24.

The R_F values for the peptides were obtained from a hydrolysis of polylysine (20 mg.) in constant-boiling hydrobromic acid (1 c.c.), kept for 8 days at 25°. A portion (0·02 c.c.) of the solution was evaporated and then transferred to a sheet of Whatman No. 4 paper, together with solutions of lysine, and di-, tri-, tetra-, and penta-lysine. These substances were thus shown to be present in the acid hydrolysate; there were also well-defined spots above the pentalysine, probably due to hexa- and hepta-lysine.

(b) *Quantitative.* A solution of dilysine acetate in 50% aqueous *iso*propanol containing 1·22 mg. of nitrogen per c.c. was serially diluted with the same solvent to 2/3, 4/9, 8/27, and 16/81 of its original strength. Each solution (0·0054 c.c.) was placed on Whatman No. 1 paper, and the chromatogram developed overnight with the above-mentioned solvent. The positions of the spot on the dried paper were located, and the ninhydrin reaction carried out, as described by Fowden (*loc. cit.*). Each solution was then diluted with 8·0 c.c. of 50% *n*-propanol and its optical density determined in a 1-cm. cell with a Hilger Spekker absorptiometer with a yellow filter (606). Trilysine could be estimated similarly.

The equivalent weights of acids were determined by titration in methanol–benzene by Fritz and Lisicki's method (*Analyt. Chem.*, 1951, **23**, 589). Analyses were performed by Mr. G. Ingram.

A preliminary account of this work was given at the Second International Congress of Biochemistry.

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LOWER COOKHAM ROAD, MAIDENHEAD, BERKSHIRE. [*Received, August 26th*, 1952.]

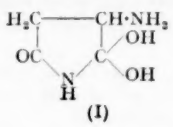
96. *The Infra-red Absorptions of Asparagine and Glutamine.*

By Mansel Davies and J. C. Evans.

In contrast to a variety of other data recently summarised by Steward and Thompson the infra-red absorptions of asparagine and glutamine do not appear to differ significantly. In particular, the cyclic formula proposed by them for asparagine finds no support in the absorptions studied.

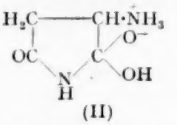
From a critical review, Steward and Thompson (*Nature*, 1952, **169**, 739) concluded that the differences in the behaviour of asparagine and glutamine are greater than would correspond to a pair of simple homologues; they proposed a new structure (*a*) for asparagine, and the properties of the two compounds were plausibly explained on the basis of this new formulation and the conventional straight-chain structure for glutamine (*b*). Steward and Thomson believe that asparagine in solution should be represented as a tautomeric system in which the equilibrium is far towards the ring form (II). Whether the new structure (I),

(*a*)



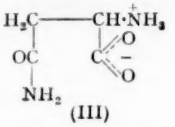
(I)

or



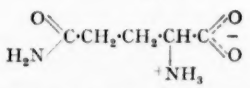
(II)

⇌



(III)

(*b*)



(IV)

having two (*gem*) hydroxyl groups in place of the conventional carboxyl structure, would have an acid strength at all comparable to the latter may be doubted but, even so, the zwitterionic form (II) must be considered as a possibility.* Part of the evidence in favour of the new asparagine structure consisted of unpublished infra-red observations by Dr. R. G. Gore. As we have been studying some of the characteristic groups in these structures (Orville Thomas, *Discuss. Faraday Soc.*, 1950, **9**, 339; Davies and Hallam, *Trans. Faraday Soc.*, 1951, **47**, 1170; Davies and Evans, *J. Chem. Phys.*, 1952, **20**, 342), crucial features in the absorptions of these compounds have been compared.

Experimental

The Grubb–Parsons S3. single-beam spectrometer equipped with silica and rock-salt prisms was used. Asparagine (a commercial sample of the hydrate from Messrs. Light) was dehydrated at 120°. We are indebted to Dr. Kenneth Bailey of the Biochemistry Department, Cambridge University, for providing us with a sample of glutamine: this might have contained a small amount of alanine but the presence of the latter would not, in any case, be expected to vitiate the comparisons being made.

Although thin films of glutamine could be prepared from the molten solid, this was not possible with asparagine without decomposition. Accordingly, mulls of the finely divided solids in carbon tetrachloride have been used. It was necessary to use different slit widths when the background and mull traces were being run in some instances: as a result, some of the detail found in the 6-μ region was unreal, arising as it did from the residual atmospheric water absorptions. These minor features are neglected in the following account. Saturated solutions of the compounds in D_2O (about 0·3M) were examined as capillary films between silver chloride windows. A small drop of concentrated hydrochloric acid (in H_2O) was added to produce an acid medium.

3-μ *Region.*—It can confidently be expected that structures (I) or (II), which contain hydroxyl groups, would absorb at higher frequencies in this region than would (IV), whose first fundamental band will be the N–H stretching frequency. In fact, both compounds, when anhydrous, show very little absorption until the latter band appears, giving rise to sharp peaks

* In a personal communication, Professor I. M. Klotz of Evanston, Ill., has pointed out the small difference in pK_a values, respectively 2·02 and 2·19 for asparagine and glutamine (see Cohn and Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, 1943, p. 84).

near 3354 cm.$^{-1}$ in asparagine and 3403 cm.$^{-1}$ in glutamine (Fig. 1) and further absorption at lower wave-numbers which merges in an ill-defined way into the CH region. In view of the absorptions of hydroxylic structures similar to (I) at wave-numbers higher than 3450 cm.$^{-1}$ (cf. Davies, *Trans. Faraday Soc.*, 1940, **36**, 1114), it is unlikely that the asparagine contains an OH group, the comparison with glutamine in Fig. 1 being virtually conclusive in this respect. The molecule of water present in asparagine hydrate shows up strongly with the absorption already having a shoulder at 3650 cm.$^{-1}$ whilst the N–H peak shifts only very slightly, from 3354 to 3358 cm.$^{-1}$ on hydration.

6-μ *Region.*—The range 1500—1750 cm.$^{-1}$ will be most significant as it includes the carbonyl and one of the carboxylate-ion stretching frequencies, ν (asymmetric) of $C\begin{matrix}O\\ \\O\end{matrix}^{-}$. Glutamine shows three well-defined absorptions—at 1690, 1639, and 1586 cm.$^{-1}$—which very probably represent respectively (see Thomas, Davies, Hallam, and Evans, *locc. cit.*), ν (C=O) of the amide

FIG. 1. FIG. 2.

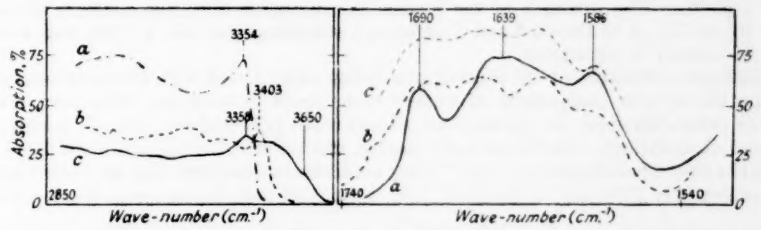


FIG. 1. *Film of* (a) *anhydrous asparagine,* (b) *anhydrous glutamine,* (c) *hydrated asparagine, all as mulls in* CCl_4.

FIG. 2. *Capillary film of* (a) *glutamine and* (b) *asparagine, and* (c) *thicker film of asparagine, all as mulls in* CCl_4.

FIG. 3. FIG. 4.

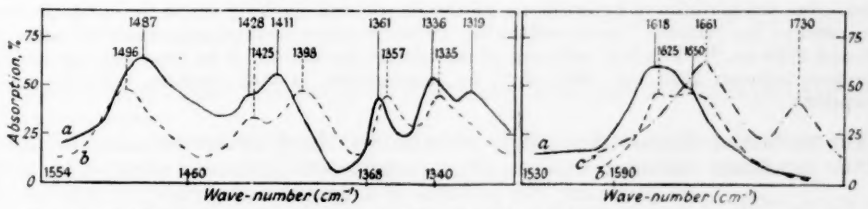


FIG. 3. *Capillary film of* (a) *glutamine and* (b) *asparagine, as mulls in* CCl_4.

FIG. 4. *Capillary film of saturated solution of* (a) *glutamine in* D_2O, (b) *asparagine in* D_2O, *and* (c) *asparagine in* D_2O *plus* HCl.

group, ν (*as*) of the carboxylate ion, and δ (NH_2) of the amide group (Fig. 2). The asparagine spectrum is not so well defined—possibly owing merely to the larger scatter of its powder in carbon tetrachloride—but three absorptions, approximately coincident with the above, have been recorded for different specimens. There is some suggestion—not always so marked as in Fig. 2—of a doublet structure to the carboxylate absorption at 1640 cm.$^{-1}$: this may arise from conditions in the crystalline solid. The δ (NH_2) frequency is now perhaps somewhat lower, at 1580 cm.$^{-1}$. It is by no means certain from our records that asparagine has an absorption centred near 1525 cm.$^{-1}$ as quoted from Gore's observations: in those instances where it appeared we are inclined to ascribe it to an atmospheric water absorption, and so it is not surprising that it also appears in some of the glutamine records.

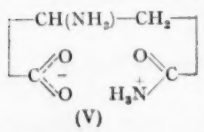
Apart from the general similarity shown in Fig. 2, the definite presence of the ν (*as*) carboxylate frequency at 1640 cm.$^{-1}$ in asparagine (cf. also the results in D_2O) again appears unfavourable to the correctness of structure (I) or (II), unless it is supposed that there is an accidental coincidence of one of the frequencies from those structures with this value: this, however, is rather unlikely, as a frequency as high as 1640 cm.$^{-1}$ almost certainly involves some double-bond character, and ν (C=O) of the amide group is already assigned to 1690 cm.$^{-1}$. Again,

the characteristic δ (NH_2) frequency appears to be present in asparagine. In the simplest terms, the asparagine absorption from 1500 to 1700 cm.$^{-1}$ is far too broad to arise solely from ν (C=O) and δ (N–H), and it is not clear what other frequency in (I) or (II) could contribute to this absorption.

6·6—7·8-μ *Region.*—For the mulls in carbon tetrachloride several well-defined absorptions are recorded in this range (Fig. 3). The differences between glutamine and asparagine are here no more than might be expected between the spectra of two homologues with the same type of structure. From the present observations the assignment of these frequencies cannot be made with certainty but, for immediate purposes, this is less significant than the apparent identity of the absorptions. Two modes δ (*as*) and δ (*s*) can be expected from the CH_2 groups : these may be 1490, and 1360 or 1335 cm.$^{-1}$, respectively. Another two absorptions are expected near 1400 cm.$^{-1}$ due to the ν (C–N) and ν (*s*) $C\overset{O}{\underset{O}{<}}^{-}$ modes : by comparison with other molecules (cf. Thomas and Hallam, *loc. cit.*) it would be plausible to assign the 1425 and 1428 cm.$^{-1}$ frequencies of asparagine and glutamine to the carboxylate group and the 1398 cm.$^{-1}$, 1411 cm.$^{-1}$ bands to ν (C–N). The presence of the former in asparagine does not conform to the new structure (I) or (II), or to Steward and Thompson's statement (*loc. cit.*, p. 742) that a band at 1420 cm.$^{-1}$ is absent in asparagine.

D_2O *Solutions.*—Because of the blurred absorption often found with solids, advantages are to be expected for the comparison of related compounds in solution. However, owing to their highly polar character, the present compounds make D_2O perhaps the only useful solvent for infra-red observations. In the carbonyl region, the absorptions are again similar, a broad band with the one centre at 1620 ± 5 cm.$^{-1}$ being found for both solutes (Fig. 4). For asparagine a second centre near 1650 cm.$^{-1}$ is probable, and a shoulder there is also seen in the glutamine absorption. These frequencies are ν (*as*) $C\overset{O}{\underset{O}{<}}^{-}$ and ν (C=O) of the amide group, respectively. This interpretation is fully confirmed by the effect of acidification, which converts $-COO^-$ into $-CO_2H$. Asparagine then very clearly shows ν (C=O) of the amide group at 1661 cm.$^{-1}$, and of the carboxylic group at 1730 cm.$^{-1}$. There appeared to be significant loss of glutamine on acidification (it is much more readily hydrolysed than asparagine, see Steward and Thompson, *loc. cit.*), but the addition of hydrochloric acid to its solution similarly led to the complete disappearance of the 1615 cm.$^{-1}$ band and the less certain (because weaker) appearance of bands at 1645 and 1729 cm.$^{-1}$. The D_2O solutions of the two solutes also failed to show any significant differences between 1530 and 1350 cm.$^{-1}$, *i.e.*, conforming, in their identity, with the solid absorptions.

The conclusions of this infra-red study are as follows : In all the features examined there is little significant difference between the asparagine and glutamine absorptions and, in particular, the presence of a normal carboxylate ion appears to be well established in the asparagine structure. Thus the particular solution of the differences between these compounds favoured by Steward and Thompson finds no support in the infra-red spectra. This may mean that some such suggestion as Dr. M. L. Huggins's, which involves a less radical structural difference between the homologues and ascribes a configuration, *e.g.*, (V), resulting from intramolecular interaction to asparagine, is more nearly the correct representation.



(V)

We thank Dr. Kenneth Bailey for the glutamine, the D.S.I.R. for a Maintenance Award (to J. C. E.), and the Chemical Society for a Research Grant.

THE EDWARD DAVIES CHEMICAL LABORATORIES,
ABERYSTWYTH.

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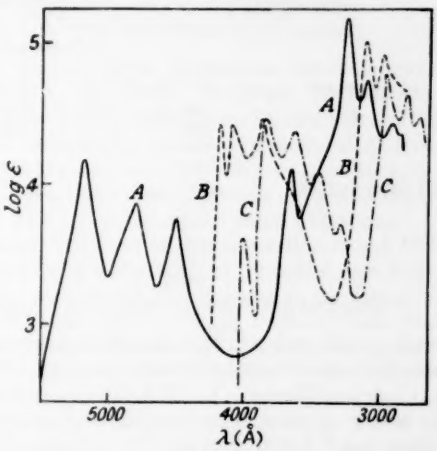
97. 8 : 9-*Benzonaphtho*(2′ : 3′-3 : 4)*pyrene.*

By John Frederick Grove.

The yellow hydrocarbon, m. p. 320°, obtained by Schroeter (*Ber.*, 1924, **57**, 1990) by the action of aluminium chloride on octahydroanthracene, has been dehydrogenated to a red hydrocarbon $C_{28}H_{16}$, shown on spectroscopic evidence to be 9 : 10-benzonaphtho(2′ : 3′-4 : 5)pyrene (III). The yellow hydrocarbon is the corresponding terminal octahydro-compound (II).

Schroeter (*Ber.*, 1924, **57**, 1990) observed that treatment of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene (octhracene) with 5% anhydrous aluminium chloride for a short time at 80° yielded a mixture of unchanged octahydroanthracene (45%), 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydrophenanthrene (octanthrene) (45%), dodecahydrotriphenylene, a viscous, high-boiling oil, and a yellow hydrocarbon, m. p. 320°. Repetition of this work has confirmed

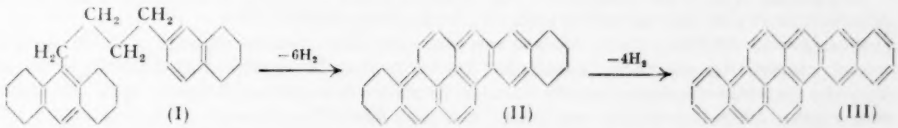


Ultra-violet absorption spectra.

A, 8 : 9-*Benzonaphtho*(2′ : 3′-3 : 4)*pyrene* (III).
B, *The octahydro-derivative* (II) *of* (III).
C, 3 : 4-*Benzopyrene.*

Schroeter's results apart from the yields of products, other than octahydrophenanthrene, which were lower.

Dehydrogenation of the yellow hydrocarbon $C_{28}H_{24}$ with palladium–charcoal gave 4 mols. of hydrogen and a red hydrocarbon $C_{28}H_{16}$. The ultra-violet absorption of this



compound (see Figure) was in excellent agreement with that calculated (Table 1) according to Clar's empirical methods (*Ber.*, 1936, **69**, 607, 1671; 1940, **73**, 81) for the hitherto undescribed 8 : 9-benzonaphtho(2′ : 3′-3 : 4)pyrene (III). As might be expected from this correlation, the value (in cm.$^{-1}$) for the lowest-frequency absorption band of the red hydrocarbon also fits correctly into the missing place between 3 : 4-8 : 9-dibenzopyrene and dinaphtho(2′ : 3′-3 : 4)(2″ : 3″-8 : 9)pyrene in the scheme drawn up by Cook, Schoental, and Scott (*Proc. Phys. Soc.*, 1950, **63**, *A*, 592).

Table 1. *Calc. for* 8 : 9-*benzonaphtho*(2′ : 3′-3 : 4)*pyrene according to Clar.*

Group	R (cm.$^{-1}$)	K (calc.)	$K^2/R = \lambda$ (Å)	Found : λ (Å)
p	$1{\cdot}0865 \times 10^6$	7·5	5177	5160
oβ	$3{\cdot}208 \times 10^6$	$10{\cdot}2 \pm 0{\cdot}1$	3180—3308	3250

It follows that the yellow hydrocarbon is the corresponding 1″ : 2″ : 3″ : 4″ : 5′ : 6′ : 7′ : 8′-octahydro-derivative (II) and in confirmation of this the ultra-violet absorption spectrum

(Figure) closely resembles that of 3 : 4-benzopyrene, the bands being shifted slightly towards longer wave-lengths. The fluorescence spectrum of (II) is also similar to that of 3 : 4-benzopyrene, the bands being shifted by 1000 cm.$^{-1}$ towards the red in quantitative agreement with the available data on pyrene and 1′ : 2′ : 3′ : 4′-tetrahydro-3 : 4-benzopyrene (Table 2). The spacings between the bands in the fluorescence spectra and between the

TABLE 2.

Ultra-violet spectra (in benzene).

Compound	$\nu \times 10^{-2}$ (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	log ε	Compound	$\nu \times 10^{-2}$ (cm.$^{-1}$)	$\Delta\nu$ (cm.$^{-1}$)	log ε
(III)	193·8		4·15	(II)	240·4		4·40
	208·0	1420	3·87		245·0	1390	4·42
	222·2	1420	3·75		258·9		4·50
	273·2		4·10		320·8		5·00
	307·7		5·17		334·7	1390	4·90
	322·2	1450	4·74				
	344·2		4·43				
	351·8		4·34				

Fluorescence spectra.

Compound	$\nu \times 10^{-2}$ (cm.$^{-1}$)	Compound	$\nu \times 10^{-2}$ (cm.$^{-1}$)	Shift due to $-[CH_2]_4-$ (cm.$^{-1}$)
Pyrene [a]	268·5	1′ : 2′ : 3′ : 4′-Tetrahydro-	263	550
	264	3 : 4-benzopyrene [a]	250	—
	261		—	—
	258		—	—
3 : 4-Benzopyrene [a]	248	(II)	237·8	2 × 510
	234		224·2	2 × 490
	220·5		210·5	2 × 500
(III) [b]	190·5		—	—
	177·0		—	—
	163·1		—	—

[a] Schoental and Scott (*J.*, 1949, 1683); solution in light petroleum. [b] Solution in benzene.

bands in each group in the absorption spectra are constant within the limits of experimental error for both (II) and (III) and are close to the expected value of 1400 cm.$^{-1}$.

Cook and Hewett (*J.*, 1933, 398) suggested that the formation of 3 : 4-benzopyrene by the action of aluminium chloride on tetrahydronaphthalene arose by dehydrogenation of 1-phenyl-4-1′-tetralylbutane. By a similar process (I) (from 2 mols. of octahydroanthracene) could give rise to the octahydrobenzonaphthopyrene (II).

EXPERIMENTAL

M. p.s are uncorrected. Microanalyses are by Weiler and Strauss, Oxford.

Ultra-violet Absorption Spectra.—These were obtained by using a Hilger medium quartz spectrograph in conjunction with a Spekker spectrophotometer.

Fluorescence Spectra.—Light from a mercury arc, after passing through a filter and lens system, entered the quartz cell containing the solution to be examined at right angles to the slit of the spectrograph and a few mm. from it. Exposures varied from 5 min. to 1½ hr. Solutions were approx. 10^{-5}M in benzene: excitation radiation 3650 Å.

1″ : 2″ : 3″ : 4″ : 5′ : 6′ : 7′ : 8′-*Octahydro*-8 : 9-*benzonaphtho*(2′ : 3′-3 : 4)*pyrene* (II). The brown gummy residue, b. p. >160°/1·5 mm. (approx. 10 g.), from the treatment of 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydroanthracene (70 g.) with anhydrous aluminium chloride (3·82 g.) for 3 hours at 90° (cf. Schroeter, *loc. cit.*) was digested with ether (100 ml.) and set aside for some hours. The yellow insoluble residue (3·7 g.) was sublimed at 280°/1 mm. The sublimate, colourless prisms (1·0 g.), m. p. 232°, from benzene–acetic acid, was identified as dodecahydrotriphenylene by dehydrogenation (5·8 mols. of hydrogen evolved) to triphenylene, identical with an authentic specimen. The unsublimed residue (2·7 g.) crystallised from benzene in yellow plates, m. p. 320° (1·0 g.), of 1″ : 2″ : 3″ : 4″ : 5′ : 6′ : 7′ : 8′-*octahydro*-8 : 9-*benzonaphtho*(2′ : 3′-3 : 4)*pyrene* [Found: C, 93·2; H, 6·8%; *M* (Rast), 393. $C_{28}H_{24}$ requires C, 93·3; H, 6·7%; *M*, 360]. It showed an intense violet fluorescence in benzene.

8 : 9-*Benzonaphtho*(2′ : 3′-3 : 4)*pyrene* (III).—The above yellow hydrocarbon (0·16 g.), when heated at 320—350° in the presence of palladised charcoal (0·03 g.) in carbon dioxide, evolved 3·8 mols. of hydrogen. The dark red residue crystallised from a large volume of hot toluene in red plates (0·10 g.) of 8 : 9-*benzonaphtho*(2′ : 3′-3 : 4)*pyrene*, m. p. 338—339° (Found: C, 95·1;

H, 4·9. $C_{28}H_{16}$ requires C, 95·4; H, 4·6%). It showed an intense green fluorescence in benzene.

I gratefully acknowledge the encouragement and advice received from the late Dr. A. F. Titley and the late Prof. A. J. Allmand during this work which was carried out at King's College, Strand, London, in 1944. I am indebted to Imperial Chemical Industries Limited for a grant and for a gift of octahydroanthracene.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES, THE FRYTHE, WELWYN, HERTS. [*Received, October 7th*, 1952.]

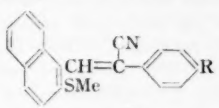
98. *Methyl β-Naphthyl Sulphide.*

By NG. PH. BUU-HOÏ, NG. HOÁN, and D. LAVIT.

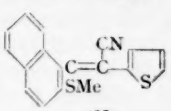
Methyl β-naphthyl sulphide undergoes reactions similar to those of the β-naphthyl ether (formylation, Friedel–Crafts reaction), although less readily. Numerous sulphur-containing naphthalene derivatives have been prepared.

IN the framework of a study of the reactivity of naphthalene derivatives, the little-known behaviour of methyl β-naphthyl sulphide has been examined. Although the *N*-methylformanilide method for aldehyde syntheses had frequently been applied to naphthyl ethers (cf. *Org. Synth.*, 1940, **20**, 12), it had not been extended to the corresponding derivatives of thionaphthols. Methyl β-naphthyl sulphide has now been found thus to give 2-methylthio-1-naphthaldehyde; its reactivity, however, was lower than that of its oxygen analogue, as witnessed by the relatively low yield (about 35%) obtained in the usual conditions.

2-Methylthio-1-naphthaldehyde was completely resistant to demethylation by pyridine hydrochloride, a characteristic shared by other thiophenol ethers (cf. Buu-Hoï and Hoán, *J. Org. Chem.*, 1952, **17**, 350) and parallel to their resistance to rearrangement (cf. Buu-Hoï, Le Bihan, Binon, and Xuong, *ibid.*, 1951, **16**, 988). In other reactions, it closely resembled its oxygen analogue. Wolff–Kishner reduction yielded methyl 1-methyl-2-naphthyl sulphide; alkali-catalysed condensation with arylacetonitriles readily gave a series of diversely substituted αβ-diarylacrylonitriles (I), and similar acrylonitriles (II) and (III) were obtained with 2-thienyl- and 3-thionaphthenyl-acetonitrile (see Table 1).



(I)



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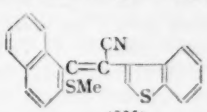

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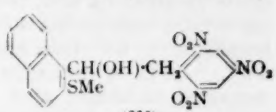
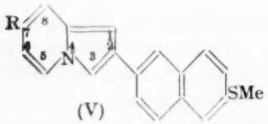


(IV)

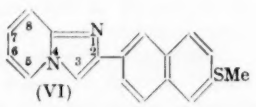
Piperidine-catalysed condensation with 2 : 4 : 6-trinitrotoluene, on the other hand, yielded, instead of the expected stilbene, the alcohol (IV), dehydration of which was probably sterically hindered. Other reactions of 2-methylthio-1-naphthaldehyde investigated were the formation of a cinchoninic acid by β-naphthylamine and pyruvic acid, preparation of a thiosemicarbazone, and, from the latter compound and α-halogenated fatty acids, of the corresponding 4-keto-2-thiazolinylhydrazones (cf. Chabrier, *Bull. Soc. chim.*, 1947, **14**, 797; Buu-Hoï and Hoán, *J.*, 1951, 1834).

In Friedel–Crafts ketone syntheses, methyl β-naphthyl sulphide closely resembled its oxygen analogue; with acetyl chloride and aluminium chloride in nitrobenzene a single ketone was obtained, which was probably 6-methylthio-2-acetonaphthone, from analogy with the behaviour of neroline in similar conditions (Haworth and Sheldrick, *J.*, 1934, 864). The other conceivable site of substitution, position 1, was excluded on the ground that the substituted naphthylamine obtained by Beckmann degradation of the ketoxime readily underwent Doebner reactions with pyruvic acid and various aldehydes to give cinchoninic acids, proof that the *ortho*-position was free. Propionylation of methyl β-naphthyl sulphide similarly gave a single ketone, probably 6-methylthio-2-propionaphthone; succinoylation yielded a keto-acid, probably β-(6-methylthio-2-naphthoyl)-propionic acid, Wolff–Kishner reduction of which afforded an acid, probably, γ-(6-methylthio-2-naphthyl)butyric acid.

Several reactions of these two ketones were studied. A Willgerodt–Kindler reaction with 6-methylthio-2-acetonaphthone gave 6-methylthio-2-naphthylacetic acid, and Wolff–Kishner reduction readily yielded 6-ethyl-2-naphthyl methyl sulphide, which could be further acetylated to a single ketone, possibly 6-ethyl-2-methylthio-1-acetonaphthone. Crude 2-ω-bromo-6-methylthioacetonaphthone, obtained by side-chain bromination in the usual way, underwent Tschitschibabin reactions with α-picoline and 2 : 4-lutidine (Tschitschibabin, *Ber.*, 1927, **60**, 1607; Borrows, Holland, and Kenyon, *J.*, 1946, 1069, 1083; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, **68**, 452) to give 2-(6-methylthio-2-naphthyl)- (V; R = H) and 7-methyl-2-(6-methylthio-2-naphthyl)pyrrocoline (V; R = Me), and with 2-aminopyridine (Tschitschibabin, *Ber.*, 1925, **58**, 1704; 1926, **59**, 2048; Tschitschibabin and Plaschenkowa, *Ber.*, 1931, **64**, 2842; Buu-Hoï and Hoán, *loc. cit.*) to give 2-(6-methylthio-2-naphthyl)glyoxalino[1 : 2-*a*]pyridine (VI). Fischer cyclisation of the phenylhydrazones of 6-methylthio-2-acetonaphthone and -2-propionaphthone gave 2-(6-methylthio-2-naphthyl)- (VII; R = H) and 3-methyl-2-(6-methylthio-2-naphthyl)-indole (VII; R = Me).



(V)



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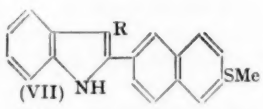

(VII)

The ketones described in this work gave positive Pfitzinger reactions; the cinchoninic acids and quinolines obtained therefrom by decarboxylation are listed in Table 2, together with the cinchoninic acids prepared by the Doebner reactions. Table 3 lists the various 4-keto-2-thiazolinylhydrazones prepared from the thiosemicarbazones of 2-methylthio-1-naphthaldehyde and 6-methylthio-2-acetonaphthone.

Experimental

2-Methylthio-1-naphthaldehyde.—Methyl β-naphthyl sulphide (30 g.), *N*-methylformanilide (28 g.), and phosphorus oxychloride (31 g.) were heated for 6 hours on a water-bath; after cooling, the product was poured on ice and taken up in toluene, and the organic layer washed with dilute hydrochloric acid, then with water, and dried (Na_2SO_4); the solvent was removed, and the residue vacuum-fractionated, giving the *aldehyde* (12 g.), b. p. 220°/20 mm., pale yellow leaflets, m. p. 65° (from ethanol) (Found: C, 71·2; H, 5·0. $C_{12}H_{10}OS$ requires C, 71·3; H, 5·0%). 18 G. of unchanged methyl β-naphthyl sulphide were recovered. The substance was recovered unchanged after 10 minutes' boiling with redistilled pyridine hydrochloride. Its *thiosemicarbazone* formed pale yellow needles, m. p. 171°, from ethanol (Found: C, 56·5; H, 4·6. $C_{13}H_{13}N_3S_2$ requires C, 56·7; H, 4·7%).

Methyl 1-Methyl-2-naphthyl Sulphide.—The foregoing aldehyde (3 g.), 85% hydrazine hydrate (3 g.), and diethylene glycol (50 c.c.) were heated at 100° for 5 minutes, then refluxed for 2 hours with potassium hydroxide (3 g.) with removal of water. After cooling, water was added, and the solid *sulphide* obtained washed and recrystallised from ethanol as leaflets (2 g.), m. p. 48° (Found: C, 76·5; H, 6·6. $C_{12}H_{12}S$ requires C, 76·6; H, 6·4%), giving a picrate as silky crimson needles, m. p. 107°, from ethanol.

1-(2-Methylthio-1-naphthyl)-2-(2 : 4 : 6-trinitrophenyl)ethan-1-ol (IV).—An equimolecular mixture of 2-methylthio-1-naphthaldehyde and 2 : 4 : 6-trinitrotoluene in ethanol was boiled with 2 drops of piperidine and left overnight; the solid *alcohol* obtained crystallised as shiny brownish needles, m. p. 81°, from ethanol (Found: C, 52·7; H, 3·5. $C_{19}H_{15}O_7N_3S$ requires C, 53·1; H, 3·5. $C_{19}H_{13}O_6N_3S$ requires C, 55·5; H, 3·2%).

6-Methylthio-2-acetonaphthone.—To an ice-cooled solution of methyl β-naphthyl sulphide (60 g.) and acetyl chloride (30 g.) in nitrobenzene (400 c.c.), finely powdered aluminium chloride (52 g.) was added in small portions with shaking; the deep red mixture was kept overnight at room temperature, then poured on ice, the nitrobenzene steam-distilled, and the residue taken up in benzene. The benzene solution was washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed, and the *ketone* vacuum-distilled, giving a product (60 g.), b. p. 222—225°/15 mm., leaflets, m. p. 120° (from ethanol), giving an orange-red colour with sulphuric acid (Found: C, 72·1; H, 5·5. $C_{13}H_{12}OS$ requires C, 72·2; H, 5·6%). The *semicarbazone* formed leaflets, m. p. 255°, from acetic acid (Found: C, 61·3; H,

5·8. $C_{14}H_{15}ON_3S$ requires C, 61·5; H, 5·6%); the *thiosemicarbazone* crystallised from ethanol as prisms, m. p. 201° (Found: C, 58·0; H, 5·3. $C_{14}H_{15}N_3S_2$ requires C, 58·1; H, 5·2%); the *oxime* formed needles, m. p. 163°, from ethanol (Found: C, 67·5; H, 5·8. $C_{13}H_{13}ONS$ requires C, 67·5; H, 5·6%).

TABLE 1. *α-Substituted β-(6-methylthio-2-naphthyl)acrylonitriles.*

α-Substituent [a]	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
Ph	145°	$C_{20}H_{15}NS$	79·6	5·0	79·7	5·0
p-C_6H_4Me	158	$C_{21}H_{17}NS$	79·8	5·3	80·0	5·4
p-C_6H_4Cl	175	$C_{20}H_{14}NSCl$	71·2	4·0	71·5	4·2
p-C_6H_4Br	172	$C_{20}H_{14}NSBr$	63·1	3·8	63·2	3·7
p-C_6H_4I	169	$C_{20}H_{14}NSI$	56·0	3·2	56·2	3·3
p-MeO·C_6H_4	150	$C_{21}H_{17}ONS$	76·0	5·3	76·1	5·1
p-NO_2·C_6H_4 [b]	196	$C_{20}H_{14}O_2N_2S$	69·3	3·8	69·4	4·0
2-Thienyl [c]	142	$C_{18}H_{13}NS_2$	70·1	4·4	70·4	4·2
3-Thianaphthyl [d]	140	$C_{22}H_{15}NS_2$	73·6	4·4	73·9	4·2

[a] The first six substances formed, from ethanol–benzene, pale yellow needles, giving a violet colour with H_2SO_4. [b] Formed, from benzene, golden-yellow needles, giving a greenish-blue colour with H_2SO_4. [c] Golden-yellow needles from ethanol; violet colour with H_2SO_4. [d] Golden-yellow needles from ethanol; dark green colour with H_2SO_4.

6-Methylthio-2-naphthylacetic Acid.—6-Methylthio-2-acetonaphthone (10 g.), sulphur (3 g.), and morpholine (12 g.) were gently refluxed for 12 hours and the product heated for 2 hours with aqueous potassium hydroxide (charcoal). After filtration and acidification with hydrochloric acid, the solid *acid* crystallised from benzene as grey-tinged prisms, m. p. 159° (Found: C, 67·0; H, 5·2. $C_{13}H_{12}O_2S$ requires C, 67·2; H, 5·2%).

6-Ethyl-2-naphthyl Methyl Sulphide.—6-Methylthio-2-acetonaphthone (15 g.), reduced by hydrazine hydrate (15 g.) and potassium hydroxide (15 g.) in diethylene glycol (200 c.c.) in the usual way, yielded a *compound* (12·5 g.), b. p. 185°/15 mm., leaflets, m. p. 48° (from methanol) (Found: C, 77·2; H, 7·1. $C_{13}H_{14}S$ requires C, 77·2; H, 6·9%); the picrate had m. p. 101° (from ethanol).

6-Methylthio-2-naphthylamine.—An ice-cooled suspension of 6-methylthio-2-acetonaphthone oxime (20 g.) in ether (200 c.c.) was shaken with phosphorus pentachloride (20 g.) for 5 minutes, and the mixture poured on ice; the precipitated *2-acetamido-6-methylthionaphthalene* formed needles, m. p. 149°, from benzene (Found: C, 67·3; H, 5·8. $C_{13}H_{13}ONS$ requires C, 67·5; H, 5·6%). *6-Methylthio-2-naphthylamine*, obtained by heating this compound (11 g.) with hydrochloric acid (150 g.) for 2 hours and basification of the resulting hydrochloride (needles, m. p. *ca.* 212°), formed grey-tinged prisms, m. p. 117°, from methanol (Found: C, 69·5; H, 6·0. $C_{11}H_{11}NS$ requires C, 69·8; H, 5·8%).

Derivatives from 2-ω-Bromo-6-methylthioacetonaphthone.—A cooled solution of 6-methylthio-2-acetonaphthone (10 g.) in chloroform was treated with bromine (2·5 c.c.) in the usual way; the ω-bromo-ketone (5 g.) formed needles, m. p. 102°, from ethanol, which were not further purified; this compound, heated with *o*-phenylenediamine in ethanol, yielded *2-(6-methylthio-2-naphthyl)quinoxaline*, yellowish prisms m. p. 179° (from benzene–ethanol) (Found: C, 75·1; H, 4·7. $C_{19}H_{14}N_2S$ requires C, 75·5; H, 4·6%). The ω-bromo-ketone (1 g.) and α-picoline (0·3 g.) in ethanol (15 c.c.) were heated at 50—60° for 30 minutes; after cooling, ether was added to precipitate a picolinium compound, which was collected and treated with boiling 10% aqueous sodium hydrogen carbonate; the *2-(6-methylthio-2-naphthyl)pyrrocoline* formed crystallised as sublimable (>240°) prisms, m. p. 276°, from xylene (Found: C, 78·8; H, 5·1. $C_{19}H_{15}NS$ requires C, 78·9; H, 5·2%). A similar reaction with 2:4-lutidine gave *7-methyl-2-(6-methylthio-2-naphthyl)pyrrocoline*, leaflets, m. p. 293° (from toluene) (Found: C, 79·2; H, 5·8. $C_{20}H_{17}NS$ requires C, 79·2; H, 5·6%). *2-(6-Methylthio-2-naphthyl)glyoxalino[1:2-α]-pyridine*, prepared by briefly refluxing a solution of the ω-bromo-ketone (1 g.) and 2-aminopyridine (0·3 g.) in ethanol (15 c.c.), and basification, crystallised as grey-tinged prisms, m. p. 189°, from methanol (Found: N, 9·8. $C_{18}H_{14}N_2S$ requires N, 9·7%).

2-(6-Methylthio-2-naphthyl)indole.—6-Methylthio-2-acetonaphthone phenylhydrazone (3 g.) was cautiously heated with finely powdered fused zinc chloride (3 g.) until a violent reaction set in; after cooling, the *indole* was taken up in toluene, washed with aqueous acetic acid, and recrystallised from toluene, giving grey-tinged prisms, m. p. 251°, giving a red colour with sulphuric acid (Found: C, 78·6; H, 5·0. $C_{19}H_{15}NS$ requires C, 78·9; H, 5·2%); its picrate formed violet-brown needles, m. p. 198°, from benzene.

6-Methylthio-2-propionaphthone.—To a solution of methyl β-naphthyl sulphide (50 g.) and propionic anhydride (40 g.) in nitrobenzene (400 c.c.), aluminium chloride (80 g.) was added in small portions, and the mixture kept overnight at room temperature; after the usual treatment, a *ketone* was obtained (52 g.), b. p. 232—235°/13 mm., leaflets, m. p. 100° (from ethanol), giving an orange-red colour with sulphuric acid (Found: C, 73·0; H, 6·2. $C_{14}H_{14}OS$ requires C, 73·0; H, 6·1%). The *semicarbazone* formed prisms, m. p. 217° (Found: N, 14·3. $C_{15}H_{17}ON_3S$ requires N, 14·6%), and the *thiosemicarbazone* pale yellow needles, m. p. 180° (Found: C, 59·6; H, 5·6. $C_{15}H_{17}N_3S_2$ requires C, 59·4; H, 5·6%), both from ethanol.

3-Methyl-2-(6-methylthio-2-naphthyl)indole.—A solution of the phenylhydrazone (3 g.) of the foregoing ketone in acetic acid saturated with hydrogen chloride (15 c.c.) was boiled for 2 minutes, and the product poured into water, taken up in benzene, and purified by vacuum-distillation; the *indole* (2 g.) crystallised from ethanol as colourless prisms, m. p. 146°, giving a red colour with sulphuric acid (Found: C, 79·0; H, 5·8. $C_{20}H_{17}NS$ requires C, 79·2; H, 5·6%); the picrate formed silky brown-violet needles, m. p. 162°, from ethanol.

β-(6-Methylthio-2-naphthoyl)propionic Acid.—To an ice-cooled solution of methyl β-naphthyl sulphide (55 g.) and succinic anhydride (34·7 g.) in nitrobenzene (400 c.c.), aluminium chloride (95 g.) was added in small portions, and the mixture kept overnight at room temperature; after decomposition with water and steam-distillation of the nitrobenzene, the *keto-acid* (68 g.) was purified through its sodium salt, and crystallised, as needles, m. p. 171°, from benzene (Found: C, 65·5; H, 5·2. $C_{15}H_{14}O_3S$ requires C, 65·7; H, 5·1%).

TABLE 2*a*. *Substituted 2-(6-methylthio-2-naphthyl)quinolines.*[a]

Substituents (in quinoline rings)	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
(None)[b]	182°	$C_{20}H_{15}NS$	79·9	5·3	79·7	5·0
4-Carboxy	252	$C_{21}H_{15}O_2NS$	73·0	4·4	73·0	4·3
6-Methyl[c]	183	$C_{21}H_{17}NS$	79·8	5·7	80·0	5·4
4-Carboxy-6-methyl	242	$C_{22}H_{17}O_2NS$	73·4	4·6	73·5	4·7
6-Bromo-4-carboxy	276	$C_{21}H_{14}O_2NSBr$	59·2	3·3	59·4	3·3
4-Carboxy-6-chloro	270	$C_{21}H_{14}O_2NSCl$	66·3	3·5	66·3	3·7
3-Methyl[d]	138	$C_{21}H_{17}NS$	79·7	5·7	80·0	5·4
4-Carboxy-3-methyl	286	$C_{22}H_{17}O_2NS$	73·4	4·9	73·5	4·7
6-Bromo-3-methyl[e]	185	$C_{21}H_{16}NSBr$	64·2	4·0	64·0	4·1
6-Bromo-4-carboxy-3-methyl	310	$C_{22}H_{16}O_2NSBr$	60·2	3·5	60·3	3·7
3:6-Dimethyl	143	$C_{22}H_{19}NS$	80·1	6·0	80·2	5·8
4-Carboxy-3:6-dimethyl	302	$C_{23}H_{19}O_2NS$	73·7	5·0	74·0	5·1
6-Chloro-3-methyl	162	$C_{21}H_{16}NSCl$	72·3	4·8	72·1	4·6
4-Carboxy-6-chloro-3-methyl	316	$C_{22}H_{16}O_2NSCl$	66·9	4·3	67·1	4·1

[a] The cinchoninic acids formed pale yellow prisms from ethanol–toluene; the quinolines formed colourless needles from ethanol. [b] Picrate, orange-yellow prisms, m. p. 208° (decomp.), from toluene. [c] Orange-yellow picrate, m. p. 203°. [d] Orange-yellow picrate, m. p. 198°. [e] Orange-yellow picrate, m. p. 195°.

TABLE 2*b*. *2-Substituted 7-methylthio-1-azaphenanthrene-4-carboxylic acids.*[a]

2-Substituent	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
2′-Thienyl	306°	$C_{19}H_{13}O_2NS_2$	64·8	3·4	65·0	3·7
Phenyl	314	$C_{21}H_{15}O_2NS$	73·1	4·5	73·0	4·3
p-Methoxyphenyl	322	$C_{22}H_{17}O_3NS$	70·1	4·3	70·4	4·5
5′-Acenaphthyl	305	$C_{27}H_{19}O_2NS$	77·2	4·4	77·0	4·5
3′-Pyrenyl	310	$C_{31}H_{19}O_2NS$	79·0	4·3	79·3	4·1
9′-Phenanthryl	303	$C_{29}H_{19}O_2NS$	78·3	4·0	78·2	4·3
9′-Ethyl-3′-carbazolyl	306	$C_{29}H_{22}O_2N_2S$	75·0	4·9	75·3	4·8
p-Dimethylaminophenyl	325	$C_{23}H_{20}O_2N_2S$	71·0	5·5	71·1	5·2
p-Chlorophenyl	296	$C_{21}H_{14}O_2NSCl$	6·66	3·9	66·4	3·7
3′:4′-Methylenedioxyphenyl	346	$C_{23}H_{15}O_4NS$	67·6	4·2	67·9	3·9
α-Naphthyl	314	$C_{25}H_{17}O_2NS$	75·8	4·5	75·9	4·3
2′-Furyl	309	$C_{19}H_{13}O_3NS$	67·7	4·0	68·1	3·9
3′:4′-Dichlorophenyl	307	$C_{21}H_{13}O_2NSCl_2$	60·6	3·2	60·9	3·1
2′:4′-Dichlorophenyl	301	$C_{21}H_{13}O_2NSCl_2$	61·0	3·3	60·9	3·1
5′-Chloro-2′-thienyl	300	$C_{19}H_{12}O_2NS_2Cl$	58·8	3·0	59·1	3·1
2′-Methoxy-1′-naphthyl	305	$C_{26}H_{19}O_3NS$	73·3	4·8	73·4	4·5
2′-Methylthio-1′-naphthyl	304	$C_{26}H_{19}O_2NS_2$	70·4	4·1	70·7	4·3

[a] Purified by crystallisation from acetic acid or through their sodium salts. All yellow or orange-yellow needles, melting with decarboxylation.

TABLE 3. *4-Keto-2-thiazolinylhydrazones.*[a]

	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
Of 2-methylthio-1-naphthaldehyde.						
4-Keto-2-thiazolinylhydrazone	263°	$C_{15}H_{13}ON_3S_2$	57·0	4·3	57·1	4·1
5-Ethyl-4-keto-2-thiazolinylhydrazone	240	$C_{17}H_{17}ON_3S_2$	59·3	5·1	59·5	5·0
5-*n*-Tetradecyl-4-keto-2-thiazolinylhydrazone	153	$C_{29}H_{41}ON_3S_2$	68·3	8·2	68·1	8·0
5-*n*-Hexadecyl-4-keto-2-thiazolinylhydrazone	131	$C_{31}H_{45}ON_3S_2$	68·8	8·1	69·0	8·3
Of 6-methylthio-2-acetonaphthone.						
4-Keto-2-thiazolinylhydrazone	228	$C_{16}H_{15}ON_3S_2$	58·1	4·7	58·4	4·6
5-Ethyl-4-keto-2-thiazolinylhydrazone	182	$C_{18}H_{19}ON_3S_2$	60·3	5·5	60·5	5·3
5-*n*-Tetradecyl-4-keto-2-thiazolinylhydrazone	111	$C_{30}H_{43}ON_3S_2$	68·3	8·0	68·6	8·2
5-*n*-Hexadecyl-4-keto-2-thiazolinylhydrazone	95	$C_{32}H_{47}ON_3S_2$	69·0	8·5	69·4	8·5

[a] Prepared by refluxing of a mixture of the thiosemicarbazone and chloroacetic acid or an α-bromo-acid in ethanol, and recrystallisation of the precipitate from ethanol or acetic acid.

γ-(6-Methylthio-2-naphthyl)butyric Acid.—The foregoing acid (65 g.), 85% hydrazine hydrate (45 g.), and potassium hydroxide (45 g.) in diethylene glycol (400 c.c.) were refluxed for 6 hours with removal of water; after dilution with water and acidification with hydrochloric acid, the *acid* was taken up in benzene and purified by distillation at *ca.* 260°/2 mm.; it formed colourless needles (44 g.), m. p. 109°, from *cyclo*hexane (Found: C, 69·1; H, 6·5. $C_{15}H_{16}O_2S$ requires C, 69·2; H, 6·2%).

Preparation of Substituted Acrylonitriles.—An equimolecular mixture of 2-methylthio-1-naphthaldehyde and the appropriate arylacetonitrile in ethanol was shaken with some drops of a 20% aqueous solution of potassium hydroxide; the precipitated *acrylonitrile* was collected, washed, and crystallised from the appropriate solvent; in the case of 4-nitrophenylacetonitrile, piperidine was used as catalyst.

6-Ethyl-2-methylthio-1(?)-acetonaphthone.—6-Ethyl-2-naphthyl methyl sulphide (12 g.) was acetylated with acetyl chloride (5 g.) and aluminium chloride (9 g.) in nitrobenzene (100 c.c.) in the usual way; the *ketone* obtained (8 g.) had b. p. 220—224°/15 mm., and crystallised as yellowish needles, m. p. 67° (from *cyclo*hexane), giving a blood-red colour with sulphuric acid (Found: C, 73·5; H, 6·6. $C_{15}H_{16}OS$ requires C, 73·8; H, 6·6%); it gave a positive Pfitzinger reaction with isatin, and a pale yellow cinchoninic acid, m. p. 185°.

Tests showed that *in vitro*, as in previous instances (Buu-Hoï and Hoán, *J.*, 1951, 1834), the thiosemicarbazones mentioned above were fairly tuberculostatic, in contrast with the corresponding 4-keto-2-thiazolinylhydrazones.

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99. *Investigation of Polymorphism and Isomerism in Cytidine Phosphates.*

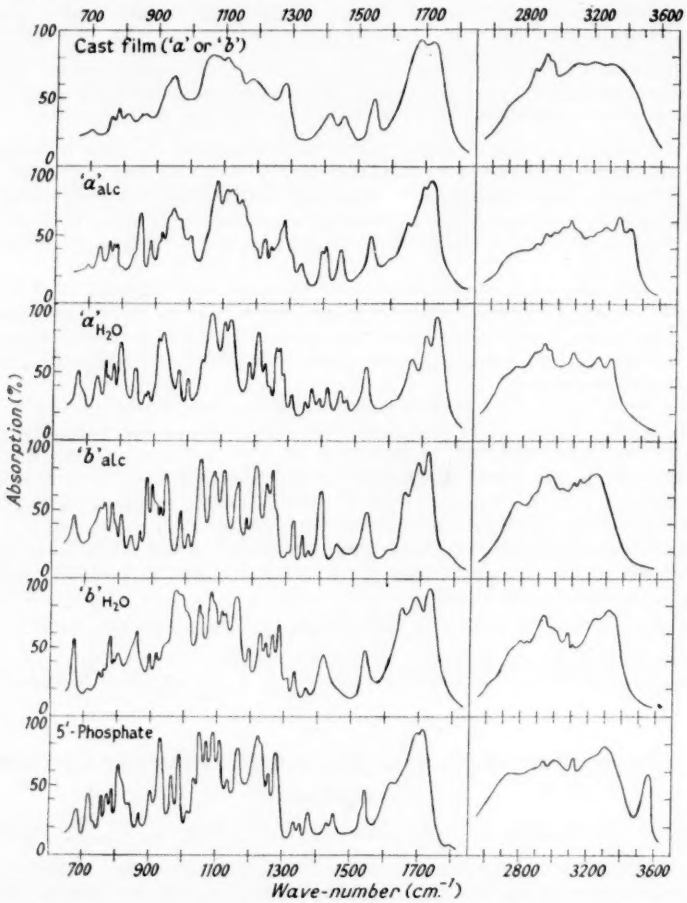
By R. J. C. HARRIS, S. F. D. ORR, E. M. F. ROE, and J. F. THOMAS.

Isolation of two isomeric cytidine phosphates from the products of hydrolysis of yeast nucleic acid is described. Each isomer has been obtained in an amorphous form and in two stable crystalline forms, and these have been characterised by their infra-red spectra. The spectra are discussed in relation to their use in analysis of mixtures of the isomers, and a quantitative method for such analysis in the solid state is presented. Ultra-violet absorption data for the two isomers are presented and the structures of the isomers are discussed.

ACID hydrolysis of yeast pentosenucleic acid, followed by removal of guanine, free acid, and free phosphate, affords a mixture of the pyrimidine nucleotides. The cytosine nucleotides may be separated as pyridine salts, leaving uracil nucleotides in solution. By ion-exchange chromatography, Cohn (*J. Amer. Chem. Soc.*, 1950, **72**, 2811) and Loring *et al.* (*ibid.*, p. 2811; 1951, **73**, 4215; *J. Biol. Chem.*, 1952, **196**, 807) obtained two isomeric

cytidylic acids, designated " a " and " b," from hydrolysates of pentosenucleic acids by various methods. The two cytosine nucleotides, obtained as before from an acid hydrolysate of yeast nucleic acid through their insoluble pyridine salts, have now readily been separated. Cytidylic acid " b " yields an insoluble dibrucine salt, and leaves a brucine-containing mother-liquor from which pure cytidylic acid " a " is obtained. By first separating the cytosine nucleotides from those of uracil, the isomers are separated rather than merely successively isolated by two different procedures, and further the

Plot of percentage absorption against frequency in cm.$^{-1}$ for the isomeric cytidylic acids.



uracil nucleotides are recovered free from either cytidylic acid isomer and may then themselves be obtained pure.

The progress of this separation can be followed by determination of optical rotation (Loring, *loc. cit.*) or of ultra-violet absorption spectra, especially the ratio of the optical density at 280 mμ to that at 260 mμ (Loring, Cohn, *locc. cit.*). Infra-red spectral measurements have been used in the present work; these had to be made on the solid material and were complicated by differences of physical form in the same chemical entity. Each isomer has been obtained (see Experimental section) in an amorphous form and in two crystalline forms (from aqueous alcohol or water); the latter are referred to as " a "$_{alc}$ or " a "$_{H_2O}$, etc. None of the forms contains water of crystallisation, and the two crystalline forms of each isomer are not, in general, interconvertible except through recrystallisation.

On one occasion, however, the " a " isomer was obtained from water in a metastable crystalline form, which changed into the usual " a "$_{H_2O}$ form in a few days; its spectrum is not reproduced in view of its transient nature and production on only one occasion.

The spectra are presented in the Figure; that of cytidine-5′ phosphate is of a sample kindly supplied by Dr. W. E. Cohn, who also supplied samples of his " a " and " b " isomers for comparison. Only in the case of the adenosine phosphates have the infra-red spectra been published (Brown and Todd, *J.*, 1952, 44) of nucleotides definitely known to be separated isomers. The spectrum of cytidylic acid has been reported by Blout and Fields (*J. Biol. Chem.*, 1949, **178**, 335) and by Clark (Thesis, Columbia, 1950) although in both cases the resolution was small: both spectra were obtained on samples from the Schwartz laboratories, yet are markedly different; comparison with our spectra has shown the difference to be due to crystal form, both materials being predominantly the " b " isomer.

In spite of the polymorphism, there is no difficulty in recognising the spectra or in obtaining an estimate of the amount of each isomer present in a mixture. For recognition of the forms present, the detail available in the infra-red spectrum is more characteristic than any other single property, and it suffices to examine only a small region of the spectrum, that from 1200 to 1350 cm.$^{-1}$ being the most sensitive. Furthermore, as each isomer is easily obtained in a single crystal form by crystallisation under constant conditions, the analysis reduces to that of one of four possible two-component mixtures, and is easily carried out as described below. Finally, extraneous impurities can easily be detected and allowed for, so that even in their presence the isomeric composition can be estimated.

In the analysis of solid mixtures, two difficulties appear. First, the films scatter as well as absorb the incident energy and, secondly, it is difficult to measure the amount of material absorbing. The former was overcome by measuring differences in optical density at an absorption maximum and a neighbouring minimum (Pirlot, *Bull. Soc. chim. Belg.*, 1949, **58**, 28); the amount of scatter will not affect this difference, as the percentage scatter will be approximately equal at the two positions, owing to their proximity. The second difficulty was overcome by measuring the ratio of two such differences, chosen so that the value is large for one component of the mixture and small for the other. The relation between the value of this ratio and the composition of the mixture may be obtained empirically, but is easily calculated from the value of the ratio for three different samples; the calculation and the measurements are simplified by taking for these the two pure components and a 1 : 1 mixture.

Let the extinctions of the two components, a and b, for unit thickness, be a_1 and b_1 at one frequency and a_2 and b_2 at a second. If r_a, r_b, and $r_\frac{1}{2}$ are the values of the ratio of optical density at the first position to that at the second, then $r_a = a_1/a_2$, $r_b = b_1/b_2$, and $r_\frac{1}{2} = (a_1 + b_1)/(a_2 + b_2)$, irrespective of thickness, provided that Beer's law holds.

Similarly, for a mixture of x parts of a to $(1 - x)$ parts b

$$r_x = \frac{xa_1 + (1 - x)b_1}{xa_2 + (1 - x)b_2}, \text{ whence } x = \frac{p(r_b - r_x)}{p(r_b - r_x) + (r_x - r_a)}$$

where $p = b_2/a_2 = (r_a - r_\frac{1}{2})/(r_\frac{1}{2} - r_b)$. The composition is therefore determined by the values of r_x, r_a, r_b, and $r_\frac{1}{2}$. Provided all the densities measured are below about 0·7 the assumption of Beer's law is valid, as the band-width of the band used is large compared with the resolution (Philpotts, Thain, and Smith, *Analyt. Chem.*, 1951, **23**, 268). Instead of optical densities at a single frequency, differences in optical densities, used for the reasons given above, can be used.

From their infra-red spectra, Dr. Cohn's samples of cytidylic acid " a " and " b " were found to be in the form " a "$_{H_2O}$ and " b "$_{alc}$ respectively. In order to correlate the nature of our samples with those of Loring, optical rotation figures were obtained. The " a " isomer gave $[\alpha]_D^{20}$ +19·8° (c, 0·95 in H_2O) and the " b " isomer $[\alpha]_D^{20}$ +47·2° (c, 0·97 in H_2O), with a probable error in each case of ±1·0°. These figures agree well with those of Loring (1951, *loc. cit.*), who also reported some crystal data; both isomers were quoted as having oblique extinction, being therefore biaxial, but only two refractive indices were given for

each, and these were noted to be " for crystals obtained from water or aqueous alcohol." We have not attempted to carry out an exhaustive determination of the crystal data but have measured extinction angles and found straight extinction in all cases, with the possible exception of the " a "$_{H_2O}$ form, which shows a value not greater than 2° (the error of measurement being about ±1°). The alcohol forms crystallised in needles and the water forms in plates—the " b "$_{H_2O}$ form has readily given flat crystals about 2 × 4 mm.

The ultra-violet absorption spectra of cytidylic acid isomers and mixtures have been measured at various stages during chemical separation in 0·01N-HCl, 0·01N-NaOH, and in 0·05M-phosphate buffer of pH 7·0. The complete data for the " a " and " b " isomers are given in the Table.

Loring *et al.* (1952, *loc. cit.*, Fig. 1) reported the first maximum for each isomer, in acid solution, and noted its higher extinction value in the spectrum of the " b " isomer. Our repeated measurements have confirmed that this difference, together with the small wave-length differences at maxima and minima, are significant. The additional data (see Table) for alkaline and pH 7·0 buffer solutions, including that for the hitherto unreported band at low wave-lengths, further distinguish the two sets of spectra. The short-wave-length band is broader and differences between the isomers are less clearly defined in alkali and phosphate than in acid solutions, and the data for alkali and phosphate are in parentheses in the Table. Measurement of the spectrum of Cohn's cytidine-5′ phosphate shows its resemblance to that of the " b " rather than that of the " a " isomer, with a further 5—10 Å shift to longer wave-lengths for the first maximum in the 5′-phosphate, at each pH value. Its $\varepsilon_{280}/\varepsilon_{260}$ value (0·01N-HCl) is 2·1, compared with 1·99 and 1·83 for the " b " and " a " isomer respectively.

Ultra-violet absorption data.

		Cytidylic acid " a "			Cytidylic acid " b "		
		0·01N-HCl	0·01N-NaOH	Buffer pH 7·00	0·01N-HCl	0·01N-NaOH	Buffer pH 7·00
1st Max.	mμ	278	270	270	279·5	270·5	271
	ε	12,740	8,890	8,860	13,400	9,350	9,400
Min.	mμ	240·5	251·5	250·5	241	250	250
	ε	2,030	6,980	6,910	1,750	6,750	6,840
2nd Max.	mμ	211·5	(232)	(232)	212·5	(231)	(230)
	ε	10,520	(8,270)	(8,140)	10,150	(8,300)	(8,330)

The hydrolysis of the " a " and " b " cytidylic acids to cytidine (Loring *et al.*, *J. Biol. Chem.*, 1952, **196**, 821) is consistent with their formulation as cytidine phosphates; both resist oxidation by periodate and therefore cannot have the phosphate in the 5′-position. This leaves the 2′- and 3′-positions as possibilities, and Loring *et al.* (1952, *loc. cit.*, p. 827) have suggested tentatively a 2′-phosphate structure for the " a " isomer on the basis of its lower solubility, acidity, and ultra-violet absorption maximum. They suggest that these physico-chemical differences would result from a greater tendency to zwitter-ion formation, deduced from examination of an atom model of the 2′-isomer.

The progressive long-wave-length shift from the " a " to the " b " to the 5′-phosphate spectrum observed in the present investigation, taken together with evidence of the spectroscopic effects of hindrance to resonance interaction between the phenyl and pyrimidine rings in phenylpyrimidine derivatives (Maggiolo and Russell, *J.*, 1951, 3297), provides some support for these conclusions.

Experimental

A mixture of pyrimidine nucleotides prepared by acid hydrolysis of yeast ribonucleic acid (50 g.) (Pharmaco-Chemical Products Ltd.) by the method of Barker *et al.* (*J.*, 1949, 904) was separated into insoluble pyridine cytidylates and soluble pyridine uridylates by extraction with ice-cold pyridine.

Cytidylic Acid Fraction.—The pyridine cytidylate was dissolved in water (300 ml.) and evaporated to a syrup (100 ml.) under reduced pressure. Brucine (30 g.) in hot ethanol (30 ml.)

was then added. Separation of crystalline dibrucine cytidylate " b " began in a few minutes and was complete after 60 hours at 0°. The salt was washed with a little water, dried *in vacuo* (28 g.), and recrystallised from 35% aqueous alcohol (225 ml.). 24 G. were obtained.

Cytidylic Acid " b."—Dibrucine cytidylate " b," suspended in water (20 pts. by wt.), was heated to 85°. Ammonia solution (*d* 0·880) was then added (1 ml. per g. of salt). The solution was cooled to room temperature and free brucine removed by filtration. This precipitate was re-extracted with ammonia in the same way. The combined solutions were extracted with chloroform until free from brucine and evaporated *in vacuo* to low volume (*ca.* 2 ml. per g. of original salt). Diammonium cytidylate " b " was not isolated and the solution was used for the next stage.

To the solution of diammonium salt, sufficient 25% lead acetate solution was added to ensure complete precipitation. The lead cytidylate was collected by centrifugation and the deposit washed twice with water. The salt was resuspended in water and decomposed with hydrogen sulphide. The lead sulphide was removed and washed. The combined filtrates, freed from hydrogen sulphide by filtration, were concentrated *in vacuo*. Crystalline cytidylic acid " b " separated. 450 Mg. of this was recrystallised by dissolving it in 19 ml. of boiling water and adding 20 ml. of boiling ethanol: this gave 330 mg. of cytidylic acid " b," decomp. 232—233° (determined with an electrically heated m. p. apparatus, 1-mm. sealed tube put in the block at 230°; heating of 2° per minute). The nucleotide showed $[\alpha]_D^{20}$ +47·2° (*c*, 0·97 in H_2O) (Found, in anhyd. material: N, 13·15; P, 9·8. Calc. for $C_9H_{14}O_8N_3P$: N, 13·0; P, 9·6%).

Cytidylic Acid " a."—The filtrate (150 ml.) from dibrucine cytidylate " b " was concentrated *in vacuo* to 50 ml. The brucine was removed by addition of ammonia, followed by extraction with chloroform, and diammonium cytidylate " a " converted into the free nucleotide as described above. 250 Mg. of this cytidylic acid " a " gave 160 mg. after recrystallisation from 33% ethanol. The nucleotide melted at 235—236° (decomp.) (conditions described above), and showed $[\alpha]_D^{20}$ +19·8° (*c*, 0·95 in H_2O) (Found, in anhyd. material: N, 12·8; P, 9·95%).

Production of the Polymorphic Forms.—The forms described above are respectively " b "$_{alc}$ and " a "$_{alc}$. The amorphous forms were prepared by drying aqueous solutions rapidly over P_2O_5 *in vacuo*. To obtain the $_{H_2O}$-forms, saturated solutions of the respective isomers were prepared in distilled water, *viz.*, about 1% for the " a " and about 3% for the " b " isomer. The solution was then filtered and set aside on a watch-glass; a small amount of crust was formed round the edges and simultaneously crystals began to form in the solution. When the volume of solution had been reduced to about a quarter, the liquid was poured off and filtered and the resulting crystals were washed with aqueous alcohol, then absolute alcohol. Examination of the crust showed it to be in the $_{alc}$-form; two processes were therefore taking place simultaneously, true crystallisation depositng the $_{H_2O}$-forms from the body of the solution and evaporation of water leaving the $_{alc}$-forms at its edge. This suggests that the commencement of crystallisation is easier for the $_{alc}$-forms, the $_{H_2O}$-forms only being produced if sufficient time is allowed for crystallisation centres to arise.

The forms obtained from mixtures, by crystallisation from aqueous alcohol, depend partly on the composition. The less soluble " a " isomer always crystallises in the " a "$_{alc}$ form, but the more soluble " b " isomer can crystallise in either form, the " b "$_{alc}$ form being favoured by a preponderance of the " b " isomer in the mixture or by the addition of excess of alcohol; the two " b " forms have not been found together in a mixture.

Optical-rotation Determinations.—These were made on a Schmidt and Haensch polarimeter, fitted with a three-prism polariser and with a vernier scale reading directly to 0·01°. The half shadow angle was adjusted to 5° and the standard deviation for one position was 0·007°. For each determination the blank and the solution were each measured ten times to give a probable error of the mean of 0·01°. In each case, the cell was 1-cm. long.

Infra-red Data.—These were obtained on a Perkin–Elmer 12C spectrometer fitted with 13-cycle amplifier. The spectra from 3600 to 2500 cm.$^{-1}$ were obtained with a lithium fluoride prism on mulls in a fully fluorinated oil; from 1900 to 650 cm.$^{-1}$, a rock salt prism was used on mulls in liquid paraffin, except from 1500 to 1330 cm.$^{-1}$ where the " fluorocarbon " mull was used. Scatter in the films was generally small and was allowed for by placing a treated plate of rock salt in the radiation path when recording the incident energy; this plate was ground with emery paper to give the same transmission as the film at 2000 cm.$^{-1}$, where no absorption bands are found. The accuracy of band position, expressed as wave-length deviation, remains approximately constant over the entire region at about $\pm$0·01 μ.

Infra-red Analytical Data.—In the application of the method described above, the frequencies at which the optical densities are measured are chosen so that the value of the

optical-density ratio function is as different as possible for the two compounds. The best ratios to use are:

$$\text{"a"}_{alc} + \text{"b"}_{alc}: \frac{d \text{ at } 854 - d \text{ at } 820}{d \text{ at } 806 - d \text{ at } 820} \text{ or } \frac{d \text{ at } 854 - d \text{ at } 820}{d \text{ at } 1043 - d \text{ at } 1015}$$

$$\text{"a"}_{alc} + \text{"b"}_{H_2O}: \frac{d \text{ at } 854 - d \text{ at } 805}{d \text{ at } 1044 - d \text{ at } 1028}$$

$$\text{"a"}_{H_2O} + \text{"b"}_{alc}: \frac{d \text{ at } 929 - d \text{ at } 891}{d \text{ at } 1155 - d \text{ at } 1172}$$

$$\text{"a"}_{H_2O} + \text{"b"}_{H_2O}: \frac{d \text{ at } 929 - d \text{ at } 897}{d \text{ at } 1156 - d \text{ at } 1182}$$

In each case the first frequency refers to the position of a strong band of one component where the second component absorbs only weakly; that in the numerator is for the "a" component and that in the denominator for "b," so that the ratio is large for "a," and small for "b." The second frequency refers to the position of a minimum of the strongly absorbing material, the exact position being chosen to reduce the interference of the other isomer.

Ultra-violet Absorption Data.—Hilger Uvispek and Beckman DU instruments were used. The wave-length scales had been adjusted and calibrated by means of a mercury arc and gave deviations of 0—2 Å over the region of measurement. Concentrations and cell-lengths were adjusted to give optical densities within the range 0·2—0·8, for maximum accuracy of determination of extinction coefficients.

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100. *Organosilicon Compounds. Part V.* The Reaction between Organofluorosilanes and Aluminium Halides.*

By C. EABORN.

Organosilicon fluorides have been converted into the corresponding chlorides, bromides, and iodides by reaction with the appropriate aluminium halide, and diethyl- and di*iso*propyl-difluorosilane have also been converted into the dialkylchlorofluorosilanes. The rate-determining stage of this type of reaction probably involves nucleophilic attack on silicon as well as electrophilic attack on halogen.

Disproportionation of some organosilicon halides in the presence of aluminium halides has been demonstrated.

IN Part I (*J.*, 1949, 2755) the author described the reaction of trialkylfluorosilanes and of one dialkyldifluorosilane with aluminium iodide to give the corresponding alkyliodosilanes. Fluorotri-*n*-propylsilane and solid aluminium chloride gave only impure chlorotri-*n*-propyl silane, but freshly purified aluminium chloride or bromide and triethylfluorosilane readily afforded chloro- or bromo-triethylsilane (preliminary report in Part II, *J.*, 1950, 3077). The wider applicability of the method has now been demonstrated by the success of the following conversions: $Et_3SiF \longrightarrow Et_3SiCl$ and Et_3SiBr; $Pr^i_3SiF \longrightarrow Pr^i_3SiCl$; $EtMe_2SiF \longrightarrow EtMe_2SiCl$ and $EtMe_2SiBr$; $Me_2PhSiF \longrightarrow Me_2PhSiCl$; $Ph_3SiF \longrightarrow Ph_3SiCl$; $Bu^i_3SiF \longrightarrow Bu^i_3SiBr$; $Et_2SiF_2 \longrightarrow Et_2SiFCl$, Et_2SiCl_2, and Et_2SiBr_2; $Pr^i_2SiF_2 \longrightarrow Pr^i_2SiFCl$ and $Pr^i_2SiBr_2$.

* Part IV, *J.*, 1952, 2846.

Reaction Conditions.—Although aluminium chloride was successfully used in some cases in absence of solvent, yet use of diethyl ether as solvent was more satisfactory for the preparation of the organochlorosilanes. Aluminium bromide disperses quickly and reacts when shaken with an alkylfluorosilane, and the reaction in absence of solvent was satisfactory in, *e.g.*, the conversions $Et_3SiF \longrightarrow Et_3SiBr$, and $Et_2SiF_2 \longrightarrow Et_2SiBr_2$, but where there is danger of disproportionation it is desirable to minimize the reaction temperature by use of a solvent, and ether and benzene proved satisfactory. Comparatively few common solvents are completely unaffected by boiling with aluminium halides, and care must be taken that no products from the solvent boil in the region of the organosilicon compounds under investigation. When decahydronaphthalene was used as a solvent for the conversion of diethyldifluoro- into dibromodiethyl-silane the latter compound was formed, but it could not be separated from a rearrangement product of the solvent which boiled in the same region (the formation of this product has been described by, *e.g.*, Jones and Linstead, *J.*, 1936, 616).

In spite of the presumably lower solubilities of the aluminium fluoro-chlorides, -bromides, and -iodides, it is clear that all three halogen atoms of the aluminium halides may react according to $3R_3SiF + AlX_3 \longrightarrow 3R_3SiX + AlF_3$. With aluminium chloride, however, the results indicate that all the chlorine atoms are utilized only with difficulty, and excess of this halide (when calculated according to $3R_3SiF + AlCl_3 \longrightarrow 3R_3SiCl$) is usually required to give good yields with reasonable speed. It is significant that in the reaction between triethylfluorosilane (2 mols.) and aluminium chloride (1 mol.) in ether, 72—78% of the fluoride reacted in 20 minutes and only 77—82% in 3 hours under comparable conditions. The decreasing availability of the chlorine atoms is probably mainly a solubility effect, for aluminium chlorofluorides are formed.

Preparative Value.—The method may be of value in the preparation of the silyl chlorides when the corresponding fluorides are easily prepared; *e.g.*, the excellent yield in the conversion of triethylsilyl fluoride into the chloride renders it more satisfactory than the method involving preparation of the ethoxide and reaction of this with acetyl chloride. For the preparation of organosilyl bromides and iodides, this method from fluorides is at least as convenient as that from chlorides *via* the anilides (Anderson, Seaton, and Rudnicki, *J. Amer. Chem. Soc.*, 1951, **73**, 2144; Anderson, *ibid.*, p. 5802). Perhaps the greatest value lies, however, in the formation in good yield of dialkylchlorofluorosilanes from difluoro-compounds, which are now readily available in several cases (see Parts III and IV, *J.*, 1952, 2840, 2846).

Disproportionation.—In the presence of the highly active aluminium halide catalysts, disproportionation of organosilicon halides might be expected to become serious. That it was not often encountered in this work may be due to the fact that the aluminium halide was never used in more than two-fold excess [*e.g.*, $\equiv SiF$ (2 mol.) + $AlCl_3$ (1 mol.)], so that little, if any, aluminium trichloride would remain unconverted into the less active chlorofluorides. However, pure bromodiethylfluorosilane could not be isolated by the method used for the corresponding chlorofluoride, and it appeared that if any of the first compound was formed it disproportionated, on fractionation, into diethyldifluoro- and dibromodiethyl-silane, and this could have been catalysed by aluminium halide. An attempt to make bromofluorodi*iso*propylsilane also failed. Organic compounds containing Me–Si links also disproportionate; *e.g.*, the conversion $EtMe_2SiF \longrightarrow EtMe_2SiBr$ yielded also bromotrimethylsilane; and bromoethyldimethylsilane was shown to disproportionate when boiled with aluminium bromide. The decomposition involved in the interaction of fluorodimethylphenylsilane and aluminium bromide was more complex, and benzene was identified in the products in addition to bromotrimethylsilane. [Phenyl groups are known to be split off from silcon by aluminium chloride (Evison and Kipping, *J.*, 1931, 2774) and the success of the conversion of triphenylsilyl fluoride into the chloride in ether must indicate that the aluminium halide reacts preferentially at the Si–F bond.] Catalytic effects of the aluminium chloride probably account also for the failure to convert tri*iso*butylfluorosilane satisfactorily into the chlorosilane, but chlorotriethylsilane is not decomposed by boiling with aluminium chloride.

The possibility of serious catalytic effects of the aluminium halides, particularly when

high distillation temperatures are involved, limits the preparative use of organosilicon fluorides and aluminium halides. The danger is reduced if dissolved aluminium halides are removed from a product before fractionation by adding a reactive alkylfluorosilane of suitable boiling point, as was done in the preparation of alkyliodosilanes (Part I, *loc. cit.*). This disproportionation itself, may, however, be of preparative value, and is being further investigated.

Mechanism of the Reaction.—In discussing the interaction of aluminium iodide and organofluorosilanes (Part I, *loc. cit.*) the author pointed out that lithium iodide was ineffective in the conversion, which probably was not a simple "halogen-exchange" reaction involving nucleophilic attack of iodide ion on silicon, but involved as the essential step a reaction of the type $R_3SiF + AlI_3 \longrightarrow R_3Si^+ + AlFI_3^-$. The failure of calcium chloride in acetonitrile to react with organofluorosilanes, although the solubility relations would favour the formation of calcium fluoride, confirms that the reaction is not of the "halogen-exchange" type, and it appears that the aluminium halides react in virtue of their electrophilic nature. That electrophilic attack on halogen is not the only rate-determining factor is suggested, however, by the observation that tri*iso*propylsilyl fluoride is converted into the chloride much less readily than are triethyl- and triphenyl-silyl fluorides. Under comparable conditions, with trialkylfluorosilane (2 mols.) and aluminium chloride (1 mol.) in ether, at least 72% of the triethyl compound reacts in 20 minutes whereas at most 10% of the tri*iso*propyl compound reacts in 3 hours. Even on the assumption of only a second-order reaction, with a second chlorine atom of the aluminium halide being as readily available as the first, this corresponds to a rate ratio of 200 : 1, and this is certainly a minimum value since the rate falls markedly as reaction proceeds. This low reactivity of the tri*iso*propylsilyl system accords with its comparative lack of reactivity in reactions such as hydrolysis and attack of Grignard reagents, which is to be attributed to the steric hindrance of the three large alkyl groups to nucleophilic attack on silicon. No appreciable steric hindrance would be expected to electrophilic attack on fluorine by aluminium halides, and it seems necessary to postulate that such electrophilic attack is also accompanied by a nucleophilic attack (of free or incipient halide ion) on silicon. The view that the reaction does not proceed through a siliconium ion is supported by the following facts: (i) siliconium ions, if formed at all, are much less stable than carbonium ions (Gilman and Dunn, *J. Amer. Chem. Soc.*, 1950, **72**, 2178; Hughes, *Quart. Reviews*, 1951, **5**, 245); (ii) the lower reactivity of triphenylsilyl fluoride when compared with triethylsilyl fluoride, although the triphenylsilyl system might be expected to give siliconium ions more readily than the trialkylsilyl system; (iii) the recent demonstration (Schumb and Breck, *J. Amer. Chem. Soc.*, 1952, **74**, 1754) that the reaction $SiF_4 + AlX_3$ (X = Cl or I) $\longrightarrow F_{4-y}SiX_y$ ($y = 0 \longrightarrow 4$) occurs also between the vapours, where siliconium ions would be even less likely than in solution.

Experimental

M. p.s and b. p.s are corrected.

General.—Dichloro-diethyl- and -dimethyl-silane were of "technical" grade, supplied by Midland Silicones Ltd. The aqueous hydrofluoric acid used was the 40% w/w "AnalaR" solution. Aluminium chloride was purified by sublimation, and aluminium bromide by distillation; molar quantities of these compounds are referred to the monomeric formula AlX_3.

Analyses.—Alkylbromo- and alkylchloro-silanes were analysed for halogen by adding a weighed amount to aqueous alcohol containing excess of potassium hydroxide and diluting the solution to a standard volume by addition of ethanol and water in such proportions as were necessary to give a homogeneous system. The halide ion was then determined by Volhard's method. Thiocyanates were similarly hydrolysed, and the thiocyanate was determined by titration against silver nitrate. For fluoride analyses see Part I (*loc. cit.*).

Diethyldifluorosilane.—A mixture of dichlorodiethylsilane (157 g.), ethanol (600 ml.), water (20 ml.), and aqueous hydrofluoric acid (140 ml.) was warmed under reflux for 3 hours at a few degrees below its b. p. It was then poured into excess of water, and the upper layer, after being washed with water, was dried (Na_2SO_4) and fractionated to give diethyldifluorosilane, b. p. 62·5° (91 g., 75%).

Fluorodimethylphenylsilane.—(i) A mixture of pentamethylphenyldisiloxan (12·5 g.),

ethanol (120 ml.), and aqueous-alcoholic hydrogen fluoride (30 ml.), after 5 hours' treatment as above, finally gave *fluorodimethylphenylsilane*, b. p. 162·4°, n_D^{25} 1·4110 (7 g., 80%) (Found: F, 12·3. $C_8H_{11}SiF$ requires F, 12·3%). (ii) The Grignard reagent from bromobenzene (2·5 mole), magnesium (2·6 g.-atom), and ether (750 ml.) was added during 1½ hours to dichlorodimethylsilane (240 g.) in ether (400 ml.) with vigorous stirring. The mixture was stirred for a further ½ hour, and then 10% sulphuric acid was added until two clear layers were formed. The ethereal layer was washed and dried, and liquid was distilled off until the b. p. reached 240°. The residue was added to ethanol (1 l.) containing hydrogen fluoride (350 ml.). The mixture was kept just below the b. p. for 8 hours. The fluorodimethylphenylsilane, b. p. 162·4° (200 g., 70%), was isolated as before.

The preparations illustrate the value of aqueous-alcoholic hydrofluoric acid (cf. Part IV, *loc. cit.*) in converting into fluorides siloxans containing Si–Ph bonds, which are cleaved by the ammonium fluoride–sulphuric acid reagent.

Ethylfluorodimethylsilane.—The Grignard reagent from ethyl bromide (2 moles), magnesium (2·1 g.-atom), and ether (750 ml.) was added to the dichlorodimethylsilane (1·5 moles) in ether (800 ml.) during 1 hour. The mixture was boiled under reflux for 1 hour, and 10% sulphuric acid added as above; the ethereal layer was washed, dried (Na_2SO_4), and fractionated. Diethyldimethylsilane, b. p. 93·5° (33 g., 20%), was isolated, and distillation was interrupted when the b. p. reached 145°. The residue (*ca.* 120 ml.) was warmed beneath a reflux condenser with ethanol (600 ml.) and hydrogen fluoride (200 ml.) for 5 hours just below the b. p. of the mixture; gas evolution ($SiMe_2F_2$?) was vigorous at first. The mixture was poured into excess of ice-cooled water, and the upper layer was washed, dried (Na_2SO_4), and fractionated, to give ethylfluorodimethylsilane, b. p. 50—50·5° (72 g., 45%).

Explanation of Table.—The Table lists the reactions between organofluorosilanes and aluminium chloride or bromide which do not require special description. Where a solvent was employed this was added (carefully in the case of ether) to the aluminium halide through a reflux condenser and the mixture was shaken or warmed, if necessary, until dissolution was complete. The fluoride was then added through the condenser and washed down with a little of the solvent, and the mixture was boiled under reflux for the time stated. In procedure A

Reactants (quantities, in mole)	Solvent (ml.)	Time (hr.)	Products	Notes (see p. 498)
Et_3SiF (0·33), $AlCl_3$ (0·12)	—	3½	R.F, b. p. 104—115° (5 g.); Et_3SiCl, b. p. 145° (0·22 mole)	B
Et_3SiF (0·25), $AlCl_3$ (0·10)	Et_2O (100)	1½	R.F, b. p. 108—110° (3 g.); Et_3SiCl, b. p. 145° (25 g., 65%)	A
Et_3SiF (0·25), $AlCl_3$ (0·12)	Et_2O (100)	4	Et_3SiCl, b. p. 145° (30 g., 80%) (Found: Cl, 23·6. Calc.: Cl, 23·5%)	A
Et_3SiF (0·33), $AlCl_3$ (0·13)	C_6H_6 (50)	4	R.F, b. p. 110° (16 g.); Et_3SiCl, b. p. 145° (0·14 mole)	(1)
$EtMe_2SiF$ (0·19), $AlCl_3$ (0·071) ...	Et_2O (30)	2	$EtMe_2SiCl$, b. p. 88—88·5° (14 g., 60%) (Found: Cl, 28·9. Calc.: Cl, 28·9%)	A (2)
Me_2PhSiF (0·152), $AlCl_3$ (0·0495)	Et_2O (40)	4½	$Me_2PhSiCl$, b. p. 195°, n_D^{25} 1·5065 (11 g., 45%) (Found: Cl, 20·9. Calc.: Cl, 20·9%)	B (3) (4)
Pr^i_3SiF (0·1), $AlCl_3$ (0·033)	Et_2O (60)	48	R.F, b. p. 169° (0·0225 mole); Pr^i_3SiCl, b. p. 202°, n_D^{20} 1·4518 (9 g., 0·047 mole) (Found: Cl, 18·4. Calc.: Cl, 18·4%)	B (5) (7)
Pr^i_3SiF (0·174), $AlCl_3$ (0·0592) ...	Et_2O (45)	48	R.F, b. p. 169° (0·051 mole); Pr^i_3SiCl, b. p. 202° (15 g., 0·078 mole)	B (6) (7)
Pr^i_3SiF (0·174), $AlCl_3$ (0·068) ...	Et_2O (40)	48	Pr^i_3SiCl, b. p. 202° (27 g., 80%) (Found: Cl, 18·4. Calc.: Cl, 18·4%)	B (7) (8)
Et_2SiF_2 (0·15), $AlCl_3$ (0·064)	Et_2O (50)	1	R.F, b. p. 61—63° (3·5 g.); Et_2SiFCl, b. p. 96° (7 g., 33%) (Found: Cl, 25·2. Calc.: Cl, 25·2%); Et_2SiCl_2, b. p. 128—130° (5 g.)	B
Et_2SiF_2 (0·15), $AlCl_3$ (0·119)	Et_2O (60)	2	R.F, b. p. 61—63° (2·5 g.); Et_2SiFCl, b. p. 96·5° (5 g., 25%); Et_2SiCl_2, b. p. 130° (9 g., 40%) (Found: Cl, 44·8. Calc.: Cl, 45·1%)	B
Et_3SiF (0·17), $AlBr_3$ (0·056)	C_6H_6 (40)	2	R.F, b. p. 109—110° (3 g.); Et_3SiBr, b. p. 164° (27 g., 80%) (Found: Br, 40·9. Calc.: Br, 40·9%)	B
Et_3SiF (0·25), $AlBr_3$ (0·11)	Et_2O (100)	4	R.F, b. p. 109—110° (2 g.); Et_3SiBr, b. p. 164° (35 g., 70%)	A
Bu^i_3SiF (0·1), $AlBr_3$ (0·33)	—	½	Bu^i_3SiBr, b. p. 240—243° (20 g., 70%) (Found: Br, 28·4. Calc.: Br, 28·6%)	B (9)

(see Notes) the liquid was decanted from the reaction mixture after the reflux period, combined with the ethereal washings of the residual solid, and fractionated. In B all the liquid was distilled quickly from the reaction mixture and the distillate was fractionated. " R.F " in the products column denotes the fluoride recovered.

Notes to Table. (1) Much of the aluminium chloride became coated and remained undissolved in the benzene even on boiling. (2) Chlorobenzene was used as a " chaser " in the fractionation. (3) A precipitate was formed immediately the fluoride was added to the aluminium chloride solution. The initial distillation gave (after removal of ether) 15 ml. of a slightly-fuming liquid, b. p. 50—80°, smelling of ether, and then 26 ml. at 180—196°. The latter was fractionated to give 1 ml. of a strongly-fuming liquid at 58—62° (Me_3SiCl by disproportionation ?), 5 ml. at 160—190°, and then the chlorodimethylphenylsilane. (4) Daudt and Hyde (*J. Amer. Chem. Soc.*, 1952, **74**, 386) describe this chloride as having b. p. 191°, n_D^{25} 1·5082, but Lewis and Newkirk (*ibid.*, 1947, **69**, 701) report b. p. 195°. (5) As very little solid had separated after 24 hours' refluxing, ether was distilled off until the total volume was *ca.* 30 ml. and the boiling was continued for a further 24 hours. (6) After the mixing of the reactants, ether was distilled off until the reflux temperature rose to *ca.* 50°. (7) A column of efficiency >40 plates was used in the fractionation. Gilman and Clark (*ibid.*, p. 1499) describe this chloride as having b. p. 198°/739 mm., n_D^{20} 1·4518. (8) The yield of the chlorotri*iso*propylsilane was improved by using a greater proportion of aluminium chloride; further, ether was distilled off until the reflux temperature was *ca.* 70° both after the mixing of the reactants and after 24 hours when the reflux temperature had fallen considerably. (9) The product from the initial distillation boiled over the range 205—245°, with the bulk constant at 241°; the latter was redistilled to give the yield shown. Taurke (*Ber.*, 1905, **38**, 1661) describes this bromide as being " yellowish," and having b. p. 245°, but our product was colourless.

Fluorotriphenylsilane and Aluminium Chloride.—(i) The fluoride (7 g., 0·025 mole) in ether (20 ml.) was added to aluminium chloride (0·012 mole) in ether (10 ml.). Ether was distilled off until the volume of the residue was *ca.* 15 ml., and the latter was boiled under reflux for 5 hours. The liquid was decanted and combined with the ethereal washings of the residual gel. The ether was boiled off with continuous addition of light petroleum (b. p. 40—60°) and the light petroleum solution was filtered hot. The filtrate was concentrated to *ca.* 12 ml., and on cooling and seeding it deposited colourless crystals (4·0 g., 55%), m. p. 87—92°, raised to 94·5—95·5° by recrystallization from light petroleum. The mixed m. p. with authentic chlorotriphenylsilane was undepressed. The solvent was removed from the mother-liquor, and addition of ethanol gave crystals of fluorotriphenylsilane (0·5 g.), m. p. 60—63°, raised to 63—64° by recrystallization from ethanol. A mixed m. p. with authentic fluorotriphenylsilane was undepressed, but a mixture of the product with ethoxytriphenylsilane (m. p. 66°) was completely liquid below 40°. (ii) A similar procedure, but involving 0·010 mole of aluminium chloride and 3½ hours' refluxing, gave chlorotriphenylsilane (2·5 g., 33%) and fluorotriphenylsilane (3·0 g.).

Diethyldifluorosilane and Aluminium Bromide.—(i) The fluoride (0·11 mole) was added to aluminium bromide (0·073 mole, *i.e.*, exact equivalent on basis of all bromine atoms reacting) in the form of small lumps. The mixture became hot on being shaken for a few minutes and a gel-like bulky solid formed. After ½ hour's refluxing, the liquid was distilled off, and all boiled in the range 167—172°. Redistillation from a small amount of copper powder and with protection from light gave *dibromodiethylsilane*, b. p. 168·5—169·5° (20 g., 75%) (Found: Br, 65·0. $C_4H_{10}Br_2Si$ requires Br, 65·0%). (ii) Diethyldifluorosilane (0·13 mole) was boiled under reflux with aluminium bromide (0·13 mole) in decalin (100 ml.) for 2 hours. Fractionation gave little liquid boiling below 160°, and *ca.* 60 ml. in the range 165—173°. This was refractionated, and the 30 ml. of liquid distilling in the range 163—169° (a sample of b. p. 167° contained Br, 43%. Calc. for $C_4H_{10}Br_2Si$: Br, 65%) were boiled with silver chloride (35 g.) under a fractionating column; dichlorodiethylsilane, b. p. 131° (14 g., 70%), was obtained, along with *ca.* 18 ml. of liquid, b. p. *ca.* 165—169°. This liquid, which had a strong peppermint odour, was washed with water, dried (Na_2SO_4), and redistilled; it then all boiled in the range 165—168° and had n_D^{18} 1·4548—1·4555.

Attempted Preparation of Bromodiethylfluorosilane.—(i) Diethyldifluorosilane (0·12 mole) was boiled under reflux with a solution of aluminium bromide (0·056 mole) in *o*-dichlorobenzene (40 ml.) for 1½ hours. When the liquid was distilled off, only 1 ml. boiled below 115°, and after a few ml. at 115—120°, the remainder distilled over the range 120—176°. When the distillate was fractionated, however, diethyldifluorosilane, b. p. 62° (4 g.), was obtained, followed by 0·8 g. of liquid at 115—117° (Found: Br, 37·6. Calc. for $C_4H_{10}BrFSi$: Br, 43·2%),

and then little liquid below 166°. It seems possible that Et_2SiFBr was obtained in the original distillation but underwent disproportionation on fractionation. (ii) Dibromodiethylsilane (0·07 mol.) was added to dried ammonium fluoride (0·1 mol.), and the reaction vessel connected to a fractionating column of low hold-up. When the mixture was warmed, liquid refluxed at 62°. Fractionation gave diethyldifluorosilane, b. p. 62·5° (5·2 g., 85% based on NH_4F taken), and no bromodiethylfluorosilane.

Difluorodiisopropylsilane and Aluminium Bromide.—When the fluoride (24 g., 0·158 mole) was shaken with solid aluminium bromide (17·5 g., 0·0656 mole) the mixture became only warm and the bromide dispersed only slowly. The mixture was boiled under reflux for ½ hour with occasional shaking, and the liquid was then distilled off to give *ca.* 10 ml. of liquid of b. p. 100—120°, 5 ml. of b. p. 120—160°, and 10 ml. of b. p. 200—208°. Fractionation gave: 0·75 ml., b. p. 85—102°; 10·5 g., b. p. 103° ($Pr^i_2SiF_2$); 0·75 ml., b. p. 190—202°; 15 g., b. p. 203·5—204·5°. The last fraction was *dibromodiisopropylsilane* (Found: Br, 58·0. $C_6H_{14}Br_2Si$ requires Br, 58·3%) in a yield of 62% based on unrecovered difluoride.

The identity of the dibromide was confirmed by shaking a solution of it (13 g.) in ether (60 ml.) with excess of aqueous ammonia for 10 minutes, separating and drying (Na_2SO_4) the ethereal layer, then evaporating off the ether and adding light petroleum to give needles of diisopropylsilanediol (6·3 g., 90%), m. p. 113—114°, undepressed by admixture with an authentic sample. This yield of the diol is distinctly superior to that obtained when the fluoride is hydrolysed (Part III, *loc. cit.*).

Comparative Interactions of Triethyl-, Triisopropyl-, and Triphenyl-silyl Fluorides with Aluminium Chloride in Ether.—In these experiments the relative amounts and the initial concentrations of the reactants were the same in all cases. The aluminium chloride taken would be equivalent to the fluoride in each case if two of the chlorine atoms were available.

(i) Triethyl- or triisopropyl-silyl fluoride (0·1 mole) was added through a reflux condenser to the aluminium chloride (0·05 mole) dissolved in ether, and was washed down with a small amount of ether (total vol., 25 ml.). The mixture was boiled under reflux for the time stated, and then quickly cooled. Excess of water was added carefully through the condenser, with cooling of the reaction vessel in ice–water. The ethereal layer was dried (Na_2SO_4), and most of the ether was taken off through a column packed with glass helices. The residue was fractionated through a centre-rod column with an efficiency of *ca.* 10 theoretical plates and a hold-up of 1 ml. A blank experiment confirmed that triethylfluorosilane was not appreciably decomposed during the hydrolysis of the excess of aluminium chloride. The results are summarized in the following table.

	SiR_3F	Time, min.	Fluoride recovered	Other products	Residue	Reaction, %
I	Et_3SiF (13·4 g.)	20	2·9 g., b. p. 110°	$Et_3Si{\cdot}OH$, b. p. 155—157°, 9·0 g.	0·7 g.	72—78
II	,, ,,	180	2·5 g., b. p. 110	$Et_3Si{\cdot}OH$, b. p. 155—157°, 9·5 g.	0·9 g.	77—82
III	Pr^i_3SiF (17·6 g.)	180	15·8 g., b. p. 169—171°	0·2 g., b. p. 173—180°	0·7 g.	4—10
IV	,, ,,	360	14·5 g., b. p. 169—171°	1·0 g., b. p. 172—190°	1·2 g.	8—20

(ii) Fluorotriphenylsilane (11·2 g., 0·042 mole) was added to a solution of aluminium chloride (2·7 g., 0·022 mole) in ether (10 ml.), and the mixture boiled under reflux for 2 hours. Water was then added, the ethereal layer separated, and the ether distilled off. The residue was separated into triphenylsilanol (7·3 g.), m. p. 155—156°, and fluorotriphenylsilane (3·0 g.), m. p. 62—64°, by making use of the low solubility of the former in light petroleum and of the latter in ethanol. The recovery of 3·0 g. of fluoride means that not more than 73% had reacted, and probably rather less.

In a similar procedure involving 7 g. (0·025 mole) of the fluoride, 1·7 g. (0·0127 mole) of aluminium chloride, and ether (7 ml.) and 20 minutes' refluxing, 3·1 g. of triphenylsilanol were obtained, and 2·8 g. of the fluoride recovered. Not more than 4·2 g. (60%) of the fluoride had reacted.

In a procedure modified to allow chlorotriphenylsilane to be isolated, fluorotriphenylsilane (7 g., 0·025 mole) was boiled under reflux with a solution of aluminium chloride (1·7 g., 0·0127 mole) in ether (7 ml.) for 20 minutes. The mixture was then cooled, light petroleum (b. p. 40—60°) added, and solvent distilled off (with further addition of light petroleum) during 15 minutes to remove ether and precipitate aluminium salts. The solution was filtered hot, and the filtrate concentrated to *ca.* 10 ml. and cooled. The solid which separated was recrystallized from light petroleum to give chlorotriphenylsilane (3·6 g.), m. p. 94—95°,

unchanged by admixture with authentic sample. From the mother-liquors, triphenylsilanol (1·7 g.) and fluorotriphenylsilane (0·9 g.) were isolated in the usual way. The yield of chloride corresponds to a minimum reaction of 50%, but part of this may have taken place during the boiling with light petroleum.

Ethylfluorodimethylsilane and Aluminium Bromide.—When ethylfluorodimethylsilane (23 g., 0·216 mole) was added to solid aluminium bromide (21 g., 0·0788 mole) beneath a reflux condenser the liquid boiled and the solid dispersed to a bulky gel. The mixture was warmed and shaken for 10 minutes, and then more ethylfluorodimethylsilane (1·5 g.) was added. The mixture was boiled under reflux for ½ hour and distilled; 1 ml. boiled below 100°, 2 ml. at 100—113°, and the remainder at 113—118°, and some gas was evolved in the last stages. The distillate was fractionated to give: 3·2 ml., b. p. 38—92° (with *ca.* 1 ml. at 78—83°; ? Me_3SiBr); 2·5 ml., b. p. 92—99°; and *ca.* 17 ml., b. p. 100—142°, with the bulk at 106—116°. All the liquid boiling above 92° was refractionated, to give: (i) 1 ml., b. p. 78—82°; (ii) 2·5 ml., b. p. 82—110°; (iii) 16·5 g., b. p. 110—112°, with the bulk at 110·5—111·5°; residue, 4 ml. Fraction (i) was probably bromotrimethylsilane (b. p. 80°); when it was heated in a test-tube with silver thiocyanate the reflux temperature rose quickly to 140° and then remained steady (Me_3SiNCS has b. p. 141°). Fraction (iii) was bromoethyldimethylsilane (Found: Br, 48·0. Calc. for $C_4H_{11}BrSi$: Br, 47·8%), in 44% yield.

Disproportionation of Bromoethyldimethylsilane in Presence of Aluminium Bromide.—Bromoethyldimethylsilane (13·5 g.) was boiled with aluminium bromide (0·6 g.) beneath a centre-rod fractionating column (efficiency, *ca.* 10 plates; hold-up, 1 ml.). After 1 hour the temperature of the vapour at the top of the column had fallen to 80°, and a slow take-off was begun. The boil-up and take-off rates were adjusted so that the b. p. at the top of the column did not exceed 81°, and 5·5 g. of liquid (i) of b. p. 77—81° were obtained in 12 hours. After this the b. p. could not be brought down below 83° on further boiling, and normal take-off gave: (ii) 0·7 ml., b. p. 82—86°; (iii) 1·5 ml., b. p. 136—162°; (iv) 2·2 ml., b. p. 161—166°. Fraction (i) contained only 48·5% of Br, and was thus not pure bromotrimethylsilane (Calc.: Br, 52·2%), but when 4 ml. were boiled with excess of silver thiocyanate, and the product was distilled off and redistilled, trimethyl*iso*thiocyanatosilane (2·5 g.), b. p. 141—144°, n_D^{20} 1·4812, was obtained. It seems probable that fraction (i) was mainly bromotrimethylsilane (5·5 g., 62% of theoretical according to $3Me_3EtSiBr \longrightarrow 2Me_3SiBr + Et_3SiBr$). Fraction (iv), which probably contained bromotriethylsilane, was added to ammonium fluoride; the liquid was distilled off and redistilled to give 0·3 ml. of b. p. 80—108°, and 0·7 ml. of b. p. 109—111°, n_D^{25} 1·388 (triethylfluorosilane has b. p. 110°, n_D^{25} 1·3900).

Fluorodimethylphenylsilane and Aluminium Bromide.—Fluorodimethylphenylsilane (18 g., 0·117 mole) was added to four lumps of the solid bromide (9·8 g., 0·0367 mole). The mixture was shaken beneath a reflux condenser for 10 minutes, during which all the aluminium bromide dispersed, the flask became too hot to touch, and the mixture became a thick gel. The mixture was distilled, and after 5 ml. of liquid had been removed in the b. p. range 120—180° the vapour temperature began to fall and *ca.* 12 ml. of liquid distilled at 160—165°, but with continual variation, indicating decomposition. The last liquid distilled at 220°. The total distillate was fractionated to give 11·8 g. of liquid of b. p. 78—82°, 0·4 ml. in the range 83—208°, and 1·5 g. at 208—210°, with a residue (hold-up) of 1 ml. The 208—210° fraction was probably impure *bromodimethylphenylsilane* (Found: Br, 38·0. $C_8H_{11}SiBr$ requires Br, 37·2%). The 78—82° fraction, which fumed strongly and gave much bromide ion on hydrolysis, was boiled with excess of silver thiocyanate; the liquid was distilled from the solid and fractionated to give: (i) 3·4 g., b. p. 78—83°; (ii) 0·8 ml., b. p. 83—130°; (iii) 4·8 g., b. p. 141—143°, and a residue of 1 ml. (hold-up). Fraction (iii) had n_D^{20} 1·4810 and was trimethyl*iso*thiocyanatosilane (b. p. 143·1°, n_D^{20} 1·4820 ± 0·0005; Anderson, *J. Amer. Chem. Soc.*, 1947, **69**, 3049). Fraction (i), which smelled strongly of benzene, was shaken with water, dried (KOH), and distilled; it all boiled at 77—80° and had n_D^{20} 1·4998 (benzene has b. p. 80°, n_D^{20} 1·5016). Benzene was confirmed by preparation of *m*-dinitrobenzene, m. p. and mixed m. p. 90·5°. Fraction (ii) also gave *m*-dinitrobenzene.

It thus seems probable that the 78—82° fraction (11·8 g.) in the first fractionation consisted of benzene (*ca.* 4·5 g., 50% of maximum possible) and bromotrimethylsilane (7·3 g., 61%). This amount of the bromide would theoretically give 6·2 g. of the *iso*thiocyanate, whereas 4·8 g. were obtained pure and a further 1 g. was probably contained in the hold-up and in fraction (ii).

Triisobutylfluorosilane and Aluminium Chloride.—(i) The fluoride (0·1 mole) was added to aluminium chloride (0·0335 mole) in ether (30 ml.), and the mixture boiled under reflux for

5½ hours. The liquid was filtered through glass-wool, combined with the ethereal washings of the residue, and distilled. After the ether, there were obtained 4 ml. of liquid, b. p. 60—80°, 1 ml. of b. p. 206—222°, and 26 g. of b. p. 223—230°. The last fraction, which was cloudy and slightly green, was redistilled; it all boiled in the range 220—230°, with 10 ml. at 223—225° (i) and 7 ml. at 225—228° (ii). Since the product boiled in the region expected for tri*iso*butylchlorosilane, fractions (i) and (ii) were analysed, but contained only 8·7 and 10·4% of hydrolysable chlorine, respectively (Calc. for $C_{12}H_{27}ClSi$: Cl, 14·4%).

Evidently a complex reaction had occurred, and the 220—230° fraction was unstable to aluminium chloride, for when it (18 g.) was boiled with aluminium chloride (2 g.) for 2 hours, and the mixture fractionated, there were obtained: 1 ml., b. p. 108—139°; (A), 1·5 g., b. p. 139—141°; 1 ml., b. p. 180—204°; (B), 3·2 g., b. p. 205—207°; 9 ml., b. p. 220—223°. The b. p.s of fractions (A) and (B) suggest that disproportionation into Bu^iSiCl_3 and $Bu^i_2SiCl_2$ had occurred, but this must have been accompanied by more complex decomposition since fraction (A) contained only 31% of chlorine (Calc. for $C_4H_9Cl_3Si$: Cl, 54·9%). Hydrolysis of fraction (B), by the method used in the preparation of di*iso*propylsilanediol, gave di*iso*butylsilanediol (0·9 g.).

(ii) When tri*iso*butylfluorosilane (0·1 mole) was added to excess of powdered aluminium chloride (0·037 mole), heat was developed and the bulk of solid increased. The mixture was boiled under reflux for 1 hour, then more aluminium chloride (0·5 g.) added, and boiling continued for 2 hours. Fractionation from the reaction mixture gave: 2·5 ml., b. p. 100—140°; 3·0 ml., b. p. 160—190°; 3 ml., b. p. 190—206°; and 8 ml., b. p. 206—210°. That some change was taking place during fractionation was indicated by the fact that when, during the take-off of the last fraction, the column was put under total reflux for 2 hours, the reflux temperature fell to 160°, and 1·5 ml. of liquid had to be taken off to restore the b. p. to 206°. Gas evolution occurred throughout the fractionation, and some liquid collected in the sulphuric acid traps used to exclude moisture.

Chlorotriethylsilane and Aluminium Chloride.—When chlorotriethylsilane (20 g.), b. p. 146°, was boiled with aluminium chloride (1·5 g.) beneath a centre-rod fractionating column, the reflux temperature at the top of the column remained at 146° during 4 hours. During an additional 4 hours, almost all the liquid distilled at 146°.

Ethyldimethylisothiocyanatosilane.—Chloroethyldimethylsilane (12 g.), prepared as shown in the Table, was boiled under reflux with excess of silver thiocyanate (22 g.) for ½ hour and all the liquid was then distilled off. Fractionation gave *ethyldimethylisothiocyanatosilane*, b. p. 167·6°, n_D^{25} 1·484 (11 g., 75%) (Found: CNS, 40·1. $C_5H_{11}NSSi$ requires CNS, 40·0%).

Dimethylphenylisothiocyanatosilane.—Chlorodimethylphenylsilane (7 g.) was boiled under reflux with excess of silver thiocyanate for ½ hour, during which the reflux temperature rose to 250°. The liquid was distilled off, and redistillation gave *dimethylphenylisothiocyanatosilane* (4 g., 50%) b. p. 257—259° (Found: CNS, 29·8. $C_9H_{11}NSSi$ requires CNS, 30·0%).

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101. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series.* Part I. Solvolytic Reactions.*

By I. Dostrovsky and M. Halmann.

A kinetic investigation of the solvolysis of five phosphorochloridates * and two phosphinyl chlorides in a wide range of solvents and at several temperatures is reported. The kinetic behaviour, and in particular the effects of variations in the structure, solvent, and added salts, indicate that a bimolecular mechanism operates in all these reactions.

Reactions of phosphorochloridates and phosphinyl chlorides have been studied kinetically in order to elucidate the mechanisms operating in reactions involving the phosphorus–halogen bond and to compare them with the reactions of analogous carbon compounds. Studies of solvolytic reactions are recorded in Part I, and Parts II and III deal with reactions with anionic nucleophilic reagents and with amines, respectively. The reactions are discussed in Part IV.

The compounds studied had the general formula $Cl{\cdot}PR_2O$ and included two phosphinyl chlorides (R = Me, Ph) and five phosphorochloridates (R = MeO, EtO, Pr^iO, $CH_2Ph{\cdot}O$, PhO). Apart from some measurements on the analogous phosphorofluoridates (fluorophosphonates) (Mazur, *J. Biol. Chem.*, 1946, **164**, 271; Waters and de Worms, *J.*, 1949, 926; Kilpatrick and Kilpatrick, *J. Phys. Coll. Chem.*, 1949, **53**, 1371), no kinetic study of the reactions of this class of compound has been reported. The solvolytic reactions now investigated included those in dry methanol, dry ethanol, a number of aqueous-ethanolic media, water, deuterium oxide, and wet formic acid. The results for all the members of the series in dry ethanol and 80% ethanol are presented in Tables 1 and 2.

Table 1. *First-order rate constants* (10^4k, $sec.^{-1}$) *for the solvolysis of phosphorochloridates and phosphinyl chlorides in dry ethanol and in* 80% *aqueous ethanol.*

R	Temp.	100% EtOH	80% EtOH *	R	Temp.	100% EtOH	80% EtOH *
Phosphorochloridates, $Cl{\cdot}PO(OR)_2$.							
Me	39·6°	9·5 ± 0·6	76 ± 2	Et	39·6°	5·1 ± 0·4	—
	10·1	1·3 ± 0·3	9·5 ± 0·5		25·14	1·7 ± 0·2	13·7 ± 0·5
	0	0·56 ± 0·06	3·6 ± 0·5		10·1	0·5 ± 0·1	4·1 ± 0·3
	−12·9	0·19 ± 0·03	1·31		0	0·23 ± 0·01	1·8 ± 0·1
CH_2Ph ...	39·6	11 ± 1	64 ± 1	Pr^i	63·8	—	37·1 ± 0·5
	25·2	3·5 ± 0·3	—		39·6	1·78 ± 0·03	9·5 ± 0·5
Ph	39·6	8·5 ± 0·5	—		25·2	0·61 ± 0·02	3·0 ± 0·1
	25·2	3·2 ± 0·2	63 ± 1		10·1	0·19 ± 0·02	—
	−8·5	—	4 ± 1		0	0·097 ± 0·003	—
Phosphinyl chlorides, $Cl{\cdot}PR_2O$.							
Me	−8·5	60 ± 10	—	Ph	25·2	73 ± 7	—
					−0·2	13 ± 1	—

* 80% Ethanol is the solvent obtained by mixing 4 vols. of dry ethanol with 1 vol. of distilled water.

Table 2. *Arrhenius parameters for solvolyses of phosphorochloridates and phosphinyl chlorides in dry ethanol and in* 80% *aqueous ethanol.*

R in $PR_2Cl{:}O$	Solvent	E (kcal./mole)	$10^{-6}A$ ($sec.^{-1}$)	R in $PR_2Cl{:}O$	Solvent	E (kcal./mole)	$10^{-6}A$ ($sec.^{-1}$)
OMe	100% EtOH	12·0	0·25	OPr^i	100% EtOH	12·8	0·16
	80% ,,	12·5	4·2		80% ,,	12·9	0·87
OEt	100% ,,	13·4	1·2	OCH_2Ph	100% ,,	14·6	17
	80% ,,	13·5	11	OPh	100% ,,	11·9	0·18
Ph	100% ,,	11·4	1·7				

Since in solvolytic reactions the observed reaction order is not indicative of the mechanism, other considerations must be used to show the course of the reaction (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; *Quart. Reviews*, 1951, **4**, 245). Although

* The nomenclature used in this series of papers conforms with the recent American-British agreement, Sept. 1952 (cf. *Proc.*, 1952, 138).

we have not applied all the available methods for determining the mechanism rigorously, yet from those tests which were carried out, we think there is little doubt that the solvolyses are bimolecular in all the solvents tried. This conclusion is based on considerations detailed under the three headings which follow.

(a) *Effect of Added Nucleophilic Reagents.*—Both anionic (*e.g.*, hydroxide, ethoxide, and fluoride ions) and neutral nucleophilic reagents (*e.g.*, amines) have a powerful effect on the rates of reaction of the chlorides considered. These reactions are discussed fully in the following papers, but it may be stated here that the observed reaction rates of the solvolytic reactions are in keeping with the much weaker nucleophilic character of the solvents used than of the nucleophilic reagents mentioned above.

(b) *Effect of Solvent Variation.*—The data in Tables 1 and 2 show that all the halides react more rapidly in 80% than in 100% ethanol. Changes in the solvent seem to affect primarily the frequency factor, leading to a net increase in the rate of reaction in the aqueous media. A similar situation has been noted for a number of other reactions (cf. Hinshelwood, *Trans. Faraday Soc.*, 1938, **34**, 138). To examine the effect of changes in solvent further, the solvolysis of di*iso*propyl phosphorochloridate was studied in a wider range of media. The results are summarised in Table 3 and the corresponding Arrhenius parameters are in Table 4.

TABLE 3. *Solvolysis of di*iso*propyl phosphorochloridate in various solvents.* [First-order rate constants, $k_1(\text{sec.}^{-1}) \times 10^4$.]

	Solvent									
Temp.	$H{\cdot}CO_2H$ *	100% MeOH	100% EtOH	95% EtOH	90% EtOH	80% EtOH	60% EtOH	10% EtOH	H_2O	D_2O
63·8°	—	—	—	—	—	37·1	84	—	—	—
39·60	0·06	—	1·78	—	5·53	9·5	—	—	—	—
25·14	0·008	2·44	0·61	1·41	2·03	3·0	5·8	—	81	65
10·08	—	—	0·19	—	0·65	—	—	—	—	—
0·0	—	—	0·97	—	—	—	0·63	8·6	8·6	—

* These values should be regarded as upper limits (see p. 504). No reaction could be detected in *tert.*-butyl alcohol after 7 days at 40°.

TABLE 4. *Arrhenius parameters for solvolysis of di*iso*propyl phosphorochloridate in various solvents.*

	100% EtOH	90% EtOH	80% EtOH	60% EtOH	H_2O	$H{\cdot}CO_2H$
E (kcal./mole) ...	12·8	12·5	12·8	14·1	14·4	25·5
$A \times 10^{-6}$ (sec.$^{-1}$)...	0·16	0·3	0·8	14	290	$4{\cdot}0 \times 10^6$

Change of solvent from a less aqueous to a more aqueous medium accelerates the solvolytic reactions proceeding by both unimolecular and bimolecular mechanisms. However, the effects on the former are much greater than on the latter (Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603; Dostrovsky and Hughes, *J.*, 1946, 167). The same facts were presented recently in a more quantitative manner by Winstein, Grunwald, and Jones (*J. Amer. Chem. Soc.*, 1951, **73**, 2700), who plot the logarithms of the rate constants against a function Y, which represents the ionising ability of the solvent, and obtain straight lines of different slope. Analysis of the data in Table 3 by either method leads to the conclusion that, in aqueous-ethanolic media, the effect of changes in water content on the rate of solvolysis corresponds to that expected from a bimolecular reaction; *e.g.*, a plot of the logarithms of the rate constants for ethanolic media against the corresponding Y values yields a straight line of slope 0·33, almost identical with that obtained in a similar plot for the solvolysis of ethyl bromide (0·34).

Of far greater significance is a comparison of the rates of solvolysis in formic acid and in an aqueous-ethanolic solvent of similar ionising capacity (Bateman and Hughes, *J.*, 1940, 941; Dostrovsky and Hughes, *J.*, 1946, 171; Winstein, Grunwald, and Jones, *loc. cit.*), for only in the case of a truly unimolecular solvolysis will the rate constants in the two media be similar. In solvolysis which is partly or wholly bimolecular, a change from the relatively strongly nucleophilic aqueous ethanol to the very weakly nucleophilic formic acid will lead to a great reduction in rate. For instance, methyl and ethyl bromides, which are typical of halides undergoing solvolysis by an essentially bimolecular process in aqueous ethanol, react some 200 and 80 times slower respectively in formic acid than in aqueous

ethanol of equal ionising capacity (*ca.* 40% ethanol). On the other hand, for *tert.*-butyl chloride and *neo*pentyl bromide, the rates of solvolysis change little on passing from aqueous ethanol to formic acid. This has already been used in demonstrating the unimolecular nature of the solvolysis of *neo*pentyl bromide. The reaction of di*iso*propyl phosphorochloridate with formic acid differs from the other solvolyses in that the *iso*propoxy-groups are split off in addition to the chlorine atom (cf. p. 506). In fact, in view of the high values of the activation energy and frequency factor for this reaction (cf. Table 4), it is probable that the reaction measured is the acid-catalysed hydrolysis of the ester. The rate measured can therefore be regarded as an upper limit for the rate of removal of the chlorine atom, and can be safely used for the comparison which follows. Thus, it is seen that the rate of solvolysis of di*iso*propyl phosphorochloridate decreases greatly on passing from aqueous ethanol to formic acid, a fact supporting the bimolecular mechanisms of this reaction. These arguments are summarised in Table 5.

TABLE 5. *Relative rates for solvolysis of some halides in "* 40% *" aqueous ethanol and in wet formic acid.*

Halides:	MeBr	EtBr	Bu^{t}Cl	$CMe_3 \cdot CH_2Br$	$Cl \cdot PO(OPr^i)_2$
k(40% EtOH)/k($H \cdot CO_2H$)	200 [a]	80 [a]	0·89 [b]	1·61 [c]	2060 [d]

[a] Winstein, Grunwald, and Jones (*loc. cit.*). [b] Calculated from results of Hughes (*J.*, 1935, 255) and of Bateman and Hughes (*J.*, 1937, 1187). [c] Calc. from results of Dostrovsky and Hughes (*J.*, 1946, 166, 171). [d] Lower limit, calc. from data of Table 3.

(c) *Effect of Acids, Salts, and Silver Ions.*—The absence of any marked drift in the rate constant of the solvolysis reaction with the course of reaction indicates the absence of acid catalysis (for the medium becomes acid during reaction) and the absence of a strong ionic effect. As a further check, the reactions were specifically tested for acid and salt effects by carrying out solvolyses with the initial addition of sulphuric acid and various salts. The results are listed in Table 6.

TABLE 6. *Solvolysis of di*iso*propyl phosphorochloridate in the presence of various reagents.*

Temp.	EtOH, %	Phosphorochloridate concn.	Additional component	1st-order rate constant 10^4k_1 (sec.$^{-1}$)
25·15°	100	0·09	None	0·61
25·15	100	0·08	0·10N-H_2SO_4	0·63
0	10	0·04	None	8·6
0	10	0·036	0·13N-H_2SO_4	8·3
25·15	60	0·05	None	5·7
25·15	60	0·06	0·1N-KNO_3	6·2
25·15	60	0·05	0·11N-$AgNO_3$	9·0
25·15	100	0·07	0·2N-$NaClO_4$	0·9
25·15	100	0·06	0·2N-NH_4NO_3	0·9

It has been shown on the basis of arguments similar to those used in analysing solvent effects on solvolytic reactions (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979) that addition of salts to the solvolysis medium increases both the unimolecular and the bimolecular rates of reaction and that the effect is expected to decrease in going to more aqueous solvents. Examination of the data of Table 6 shows that, as expected for a reaction between neutral molecules, a positive salt effect operates, and that it is less in the more aqueous solvent. The limited precision of the data and the lack of reference experiments precluded the use of these salt effects to differentiate between the two possible mechanisms of reaction.

The absence of acid catalysis should be particularly noted, for in the solvolysis of the phosphorofluoridates, marked acid catalysis has been observed (Waters and de Worms; Kilpatrick and Kilpatrick; *locc. cit.*). The small effect of silver ions shows the resistance of the phosphorus–halogen bond to electrophilic attack, which also is a measure of its reluctance to undergo reaction by an ionisation mechanism (cf. Dostrovsky and Hughes, *J.*, 1946, 169). That the course of reaction is indeed represented by the equation $PR_2OCl + R'OH = PR_2O(OR') + HCl$, where R = alkyl or alkoxy and R′ = H or alkyl, has been shown by examination of reaction products. Esters of phosphoric acid and of phosphinic acids have been obtained from reactions with dry alcohols. From reactions in highly aqueous solvents (*e.g.*, 10% ethanol) the free acids $PR_2O \cdot OH$ were isolated. On

the other hand, in reactions in less aqueous ethanolic media, mixtures of ester and free acid are formed, as shown by analysing the reaction mixture for chloride and hydrogen ions. Since free dialkyl hydrogen phosphates are strong acids, the excess of hydrogen ions over the chloride ions is a measure of the proportions of the reaction of the phosphorochloridate with water molecules. In this way it has been shown that in the solvolysis of di*iso*propyl phosphorochloridate in 80% aqueous ethanol the ratio of ethyl di*iso*propyl phosphate to di*iso*propyl hydrogen phosphate is 1·22. Since in this solvent the concentrations of ethanol and water are about the same (in moles/l.) this is also the ratio of the nucleophilic power of ethanol to that of water in the relevant reaction.

Experimental

M. p.s are uncorrected.

Materials.—Dialkyl phosphorochloridates. The methyl, ethyl, and *iso*propyl esters were prepared from the corresponding dialkyl hydrogen phosphites by chlorination in carbon tetrachloride (McCombie, Saunders, and Stacey, *J.*, 1945, 380) and purified by vacuum-distillation: dimethyl ester, b. p. 80—83°/23 mm. (Found: Cl, 23·5. Calc. for $C_2H_6O_3ClP$: Cl, 24·6%); diethyl ester, b. p. 28—30°/0·5 mm. (Found: Cl, 20·8. Calc. for $C_4H_{10}O_3ClP$: Cl, 20·5%); di*iso*propyl ester, b. p. 43—47°/0·5 mm. (Found: Cl, 18·0. Calc. for $C_6H_{14}O_3ClP$: Cl, 17·8%).

Dibenzyl phosphorochloridate was prepared by Sheehan and Frank's modification (*J. Amer. Chem. Soc.*, 1950, **72**, 1314) of Atherton, Openshaw, and Todd's method (*J.*, 1945, 382), and the oil finally obtained was used for the kinetic experiments without further purification. The diphenyl ester, prepared according to Brigl and Muller (*Ber.*, 1939, **72**, 2121), had b. p. 140—155°/1 mm. (Found: Cl, 13·3. Calc. for $C_{12}H_{10}O_3ClP$: Cl, 12·5%).

Dimethylphosphinyl chloride was prepared according to Kabachnik and Shepeleva (*Izvest. Akad. Nauk, U.S.S.R.*, Otdel. Khim. Nauk, 1949, **1**, 56; see also Kosolapoff and Watson, *J. Amer. Chem. Soc.*, 1951, **73**, 5466). The chloride sublimed at 0·5 mm., at an oil-bath temperature of about 150°, and condensed in the receiver as colourless crystals, m. p. 68—69° (Found: Cl, 32·2. Calc. for C_2H_6OClP: Cl, 31·5%).

NN-*Diethylphosphoramidic dichloride*, $NEt_2{\cdot}POCl_2$. To diethylamine (103 ml., 1 mole) in carbon tetrachloride (300 ml.) in a 3-necked flask cooled in brine, phosphorus oxychloride (46 ml., 0·5 mole) was added dropwise with stirring, under protection of a calcium chloride guard-tube. After several hours the solvent was evaporated, and the residual semi-solid distilled under reduced pressure, yielding 69 g. (73%) of a colourless oil, b. p. 129—133°/37 mm. (Found: Cl, 34·2. Calc. for $C_4H_{10}ONCl_2P$: Cl, 35·4%). Michaelis (*Annalen*, 1903, **326**, 129) gave b. p. 100°/15 mm. The product was used without further purification for the following reaction.

Diphenylphosphinyl chloride was prepared by Kosolapoff's modification (*J. Amer. Chem. Soc.*, 1949, **71**, 369) of Michaelis and Wegner's method (*Ber.*, 1915, **48**, 316) for the synthesis of arylphosphinic acids. The acid had m. p. 187°. Michaelis and Wegner (*loc. cit.*) gave m. p. 190°. The chloride had b. p. 165—160°/1 mm. (Found: Cl, 14·6. Calc. for $C_{12}H_{10}OClP$: Cl, 15·0%). The oil is very hygroscopic and is hydrolysed by atmospheric moisture to the acid.

Solvents for Rate Measurements.—Methanol was distilled from magnesium methoxide (Lund and Bjerrum, *Ber.*, 1931, **64**, 210). Ethanol was distilled from calcium oxide and then from sodium and ethyl phthalate (Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1106); some samples of it were shown, by titration with Karl Fischer's reagent (Mitchell and Smith, "Aquametry," Interscience Publ., 1948), to contain less than 0·01% of water. *tert.*-Butyl alcohol was refluxed with sodium and distilled. Formic acid, 98—100% (Baker and Adamson, C.P.), was recrystallised four times; its m. p. was 7·1°, so it contained 0·5—1% of water.

Phosphate esters. The phosphorochloridate, $(RO)_2POCl$, was refluxed with 10 vols. of absolute ethanol for ½ hour, then cooled; barium carbonate was added in slight excess, and the excess filtered off. The ethanol was evaporated off under reduced pressure, and the residue fractionated, yielding odourless oils. Ethyl dimethyl phosphate had b. p. 112—113°/41 mm. (Found: C, 31·2; H, 7·6. Calc. for $C_4H_{11}O_4P$: C, 31·2; H, 7·2%), n_D^{22} 1·3984, the triethyl ester, b. p. 211°/754 mm., n_D^{20} 1·4051, and the *ethyl di*iso*propyl* ester, b. p. 110—112°/25 mm. (Found: C, 46·2; H, 9·2; P, 14·5. $C_8H_{19}O_4P$ requires C, 45·7; H, 9·1; P, 14·8%), d_{25}^{25} 1·0066, n_D^{25} 1·4044. Ethyl diphenyl phosphate had b. p. 181—185°/2 mm. (Found: C, 61·4; H, 5·9; P, 10·6. Calc. for $C_{14}H_{15}O_4P$: C, 60·4; H, 5·4; P, 11·2%), d_{25}^{25} 1·185, n_D^{30} 1·5250 (Morel, *Bull. Soc. chim.*, 1899, **21**, 492, gives b. p. 211—221°/18 mm., d_0^0 1·2113).

*Di*iso*propyl hydrogen phosphate.* Di*iso*propyl phosphorochloridate (4·0 g.) was mixed with water and ethanol (9 : 1), and the solvents evaporated at 50° under reduced pressure, first with

a water-pump and finally for several hours with a high-vacuum system. The residual colourless oil, crystallised by freezing with liquid air, formed white crystals, m. p. 34° (3·3 g.) (Found: C, 39·6; H, 8·3; P, 17·0%; equiv., by potentiometric titration with NaOH and a glass electrode, 184. $C_6H_{15}O_4P$ requires C, 39·6; H, 8·2; P, 17·5%; equiv., 182). *Diisopropyl hydrogen phosphate* has not been recorded but its lead salt was prepared by Cavalier and Pros (*Bull. Soc. chim.*, 1900, **23**, 679). The guanidine salt, m. p. 156—157°, was prepared from guanidine carbonate (Wagner-Jauregg, O'Neil, and Summerson, *J. Amer. Chem. Soc.*, 1951, **73**, 5205) and precipitated by acetone.

Products of Solvolysis of Phosphorochloridates in "80%" Ethanol.—A solution of the di*iso*propyl ester (0·2336 g.) in 80% ethanol (10 ml.) was kept for 21 hours at about 25° and then required 18·50 ml. of 0·100N-NaOH (methyl-red) and 11·27 ml. of 0·100N-$AgNO_3$ (Calc.: 11·65 ml.). The excess of acidity over chloride, 18·50 − 11·27 = 7·23 ml., is equivalent to the amount of di*iso*propyl hydrogen phosphate formed. The proportion of the total reaction due to hydrolysis is thus 7·23 × 100/11·27 = 64%.

Solvolysis of Diisopropyl Phosphorochloridate in Formic Acid.—This ester (0·4963 g.) in 98% formic acid (10 ml.) in a glass-stoppered flask was kept for 6 days at 40° in a thermostat. The solvent was then evaporated off at room temp./2 mm. during 4 hours. A viscous liquid dibasic acid remained (0·2747 g.) [Found: P (as $Mg_2P_2O_7$), 31·2%; equiv., by titration with NaOH (methyl-red), 102; (phenolphthalein), 52. Calc. for H_3PO_4: P, 31·6%; equivs., 98, 49]. It gave the molybdate test for orthophosphoric acid, and in ammonia solution, gave magnesium ammonium phosphate (alkyl phosphates do not give a precipitate under these conditions; Bailly, *Bull. Soc. chim.*, 1919, **25**, 255). Thus in formic acid solution, di*iso*propyl phosphorochloridate was quantitatively decomposed into orthophosphoric acid. Since it is not certain whether the cleavage of the alkyl group preceded or succeeded the removal of the chlorine, the rate constants for this reaction presented in this paper must be regarded as upper limits only.

Kinetic Measurements.—All kinetic runs were made in thermostats controlled to better than 0·03°; those above room temperature contained water with an upper layer of paraffin, those below room temperature contained an aqueous solution of ethylene glycol and were placed in another cooled thermostat controlled to within 0·5°. The temperature of the thermostats of −8·5° and −12·9° was measured with a chromel–alumel thermocouple calibrated at the m. p. of redistilled mercury. Three methods were used for following the solvolysis: titration of the liberated chloride, titration of the liberated acid, and conductometric measurement of liberated ions.

Titration of liberated chloride. A weighed amount of the phosphorochloridate in a 25- or 30-ml. flask was placed in the thermostat, and the volume adjusted with the required solvent at the thermostat temperature. Samples of 3 or 5 ml. were stirred into 20—25 ml. of 95% ethanol which had been chilled to −20°. A stop-watch was started when the liquid of the first sample had passed a definite mark on the pipette.

The chloride-ion concentration was determined by a modification of Cavanagh's method (*J.*, 1927, 2207) with an electrode of silver wire covered by a thin layer of electrodeposited silver chloride. The reference electrode consisted of a glass tube 8 mm. in diameter, in the bottom of which was a ground-glass stopper which assured liquid contact between the contents of the tube and the solution of chloride surrounding it. The reference electrode tube contained a platinum electrode and was filled with a phosphate–citrate buffer of pH 3·2 containing some quinhydrone. As shown by Cavanagh, the P.D. between a quinhydrone electrode at pH 3·2 and a silver chloride electrode immersed in a saturated solution of silver chloride (containing equivalent amounts of Ag^+ and Cl^-) is zero. Thus at the end-point of the titration of a chloride solution with silver nitrate the potential between the electrodes vanished. The potential difference was measured with a Model H, Beckman glass-electrode pH meter. The silver electrode was connected to the terminal which was usually connected to the calomel electrode, and the platinum electrode was connected through a 160-megohm resistor in series to the other terminal. This procedure was adequate for estimating the chloride liberated from di*iso*propyl phosphorochloridate, for during the period of titration (1—2 minutes) the extent of solvolysis of this ester is very small. However, with the other phosphorus chlorides tested the rate of solvolysis is larger and the results are erratic.

Titration of liberated acid. Since tertiary amines at room temperature react very slowly with dialkyl phosphorochloridates (see Part III, *J.*, 1953, 511), a solution of triethylamine in acetone was used to titrate the acid liberated in the solvolysis. Lacmoid was used as an indicator, giving a very brilliant colour change. This method was used mainly for following the ethanolysis of the dimethyl ester (cf. also Böhme, *Ber.*, 1941, **74**, 246).

Conductivity method. Smooth platinum electrodes were sealed in the sides of 8—30-ml. Pyrex-glass volumetric flasks and connected with side-limbs containing mercury. Solvent was added to a level about 1 cm. above the electrodes, and the cell thus formed closed with a ground-glass stopper and immersed for ½ hour in the thermostat. A small drop of the chloride was added from a capillary and dissolved by shaking. At measured times the conductivity was determined with a bridge assembly of the type described by Jones and Josephs (*J. Amer. Chem. Soc.*, **1928**, **50**, 1049) with a 1300-cycles phase-shift audio-oscillator (Kunde, "Electronics Manual for Radio Engineers," McGraw Hill, 1949, p. 121). The bridge permitted measurement from 99,000 to 0·1 ohm. The output of the bridge was amplified through a peaked audio-amplifier ("Radio Amateur's Handbook," 1949, p. 127; American Radio Relay League) and detected with head-phones. Conductivity was measured by balancing condensers and resistors, giving an accuracy of at least 0·1%.

At first, the relation between conductivity and concentration of solvolysis products was determined in special measurements, and it was found that at the high dilutions used (0·001—0·01M) conductivity was, within the limits of accuracy, proportional to concentration. It was thus possible to calculate the first-order rate constants directly from the measurements of each run without introducing the further errors of an empirical calibration curve. This method gave satisfactory results for the solvolysis of phosphorus chlorides in aqueous solvents; in absolute ethanol the rate constants were less reproducible and deviations of up to ±10% were encountered. As shown by Norris, Fasce, and Staud (*J. Amer. Chem. Soc.*, 1935, **57**, 1416), the conductivity of hydrogen chloride in absolute ethanol is affected by traces of moisture and other impurities; precise results were obtained only with very elaborate precautions.

The main advantage of the conductivity method is the possibility of measurement of rates of reactions with half-lives as short as 1 minute, and use of only very small amounts of material.

Typical Determinations of First-order Rate Constants (k_1) of Solvolysis.—(a) *Hydrolysis of diisopropyl phosphorochloridate (initial concn. 0·00073M) in water at 25·14°.* (Conductivity method.) First-order rate constants $k_1 = (2{\cdot}3/t) \log (\kappa_\infty - \kappa_0)/(\kappa_\infty - \kappa_t)$, where κ_0, κ_t, and κ_∞ are the reciprocals of resistance at time zero, t, and infinity, respectively.

Time, min. ...	0	0·25	0·5	0·75	1·0	1·25	1·5	1·75	2·25	2·75	∞
Ohms	1440	1310	1210	1140	1080	1030	990	950	900	870	757
$10^4 k_1$ (sec.$^{-1}$)	—	78·0	78·4	77·1	77·3	77·8	78·1	80·8	81·2	78·6	—

Mean $k_1 = 79{\cdot}5 \times 10^{-4}$ sec.$^{-1}$.

(b) *Solvolysis of diisopropyl phosphorochloridate in 80% ethanol at 25·14°.* (Conductivity method.)

Time, min.	0	9	19	28	38	45	53	61	∞
Ohms	21,500	10,600	7300	5910	4980	4600	4200	3960	2761
$10^4 k_1$ (sec.$^{-1}$)	—	3·00	2·96	2·93	2·96	2·88	2·94	2·91	—

Mean $k_1 = 2{\cdot}96 \times 10^{-4}$ sec.$^{-1}$.

(c) *Solvolysis of diisopropyl phosphorochloridate (initial concn. 0·044M) in 80% ethanol at 25·14°.* [Titration of chloride method: $k_1 = (2{\cdot}3/t) \log (x_\infty - x_0)/(x_\infty - x)$].

Time, sec.	0	158	392	564	746	975	1466	2210	3992	∞
0·00984N-$AgNO_3$, ml.	2·04	3·03	4·50	5·39	6·46	7·60	9·66	12·37	16·61	22·88
$10^4 k_1$ (sec.$^{-1}$)	—	3·07	3·19	3·11	3·19	3·18	3·10	3·09	3·01	—

Mean $k_1 = 3{\cdot}12 \times 10^{-4}$ sec.$^{-1}$.

(d) *Solvolysis of diisopropyl phosphorochloridate (0·088M) in absolute ethanol at 25·14°.* (Titration of chloride method.)

Time, sec.	0	390	715	1300	1761	3067	5439	∞
0·00984N-$AgNO_3$, ml.	3·31	4·40	5·13	6·60	7·79	10·70	15·84	45·70
$10^4 k_1$ (sec.$^{-1}$)	—	0·66	0·61	0·62	0·63	0·62	0·64	—

Mean $k_1 = 0{\cdot}62 \times 10^{-4}$ sec.$^{-1}$.

(e) *Solvolysis of diphenylphosphinyl chloride (0·0016M) in absolute ethanol at 25·14°.* (Conductivity method.)

Time, min.	0	1·0	1·5	2·0	3·0	4·0
Ohms	13,000	84,000	7500	6900	6210	5810
$10^4 k_1$ (sec.$^{-1}$)	—	74·0	74·1	72·6	70·3	69·6

Mean $k_1 = 72 \times 10^{-4}$ sec.$^{-1}$.

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102. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part II.* Reaction of Diisopropyl Phosphorochloridate with Anionic Reagents.*

By I. Dostrovsky and M. Halmann.

The reactions of di*iso*propyl phosphorochloridate with a number of anions were studied in ethanolic solution. The reactions were of first order with respect to both the ester and the anion concentration. The effects of structural variations and of changes in solvent are in agreement with a simple bimolecular mechanism.

In continuation of our kinetic investigation of the phosphorochloridates (Part I *), we have studied the reactions of the *iso*propyl ester with ethoxide, phenoxide, thiophenoxide, fluoride, and acetate ions, all in ethanolic solution. These reactions are complicated by simultaneous solvolysis, and where necessary the observed rate constants were corrected for this reaction by Moelwyn-Hughes's method (*Proc. Roy. Soc.*, 1949, *A*, **196**, 540).

The reactions with thiophenoxide and acetate ions are probably slower that those with ethanol, for no increase in the rate is observed on addition of these ions to the solvolysis mixture. The order of reactivity can be written as $F^- > EtO^- > PhO^- > EtOH$, PhS^-, $CH_3{\cdot}CO{\cdot}O^-$. The reactions with ethoxide ion and fluoride ion were investigated in detail. They are irreversible, proceeding according to the equation $(RO)_2POCl + OEt^-$ (or F^-) $\longrightarrow$ $(RO_2)PO(OEt)$ [or $(RO)_2POF$] + Cl^-, are of first order with respect to both phosphorochloridate and reagent, and appear to be simple bimolecular substitution reactions. The rates for various initial concentrations of the reactants are shown in Table 1. From the temperature dependence of the reaction rates, the Arrhenius parameters were calculated and are given in Table 2.

Table 1. *Reaction of diisopropyl phosphorochloridate in dry alcohol at* 0°. (Second-order rate constants.)

With ethoxide ions.					
Initl. concn. of $Cl{\cdot}PO(OPr^i)_2$, mole/l.	0·01	0·025	0·04	0·01	
,, ,, OEt^-, mole/l.	0·02	0·02	0·02	0·097	
k_2, l. mole^{-1} sec.$^{-1}$	0·010	0·011	0·010	0·014	
With fluoride ions.					
Initl. concn. of $Cl{\cdot}PO(OPr^i)_2$, mole/l.	0·0063	0·0050	0·0052	0·0053	0·014
,, ,, F^-, mole/l.	0·0029	0·0064	0·0098	0·0098	0·023
k_2, l. mole^{-1} sec.$^{-1}$	0·034	0·031	0·027	0·035	0·027

Table 2. *Second-order rate constants at various temperatures for the reactions of diisopropyl phosphorochloridate, and the corresponding Arrhenius parameters.*

Reagent	k_2, l./mole^{-1} sec.$^{-1}$ at: 25°	0°	−8·5°	E, kcal./mole	$10^{-9}A$, l. mole^{-1} sec.$^{-1}$
NaOEt	0·11	0·010	0·0061	13·9	2·1
KF	0·23	0·030	—	12·9	0·64
NaOPh	—	0·003	—	—	—

Attempts to study the effects of changes of the alkyl group R were made but the rate of the reaction of diethyl phosphorochloridate was almost too fast to be measured and only approximate second-order rate constants were obtained. For reactions in ethanol at 0°, these were (in l. mole^{-1} sec.$^{-1}$) $k_2 = 0{\cdot}26$ for the reaction with ethoxide ions and $k_2 = 0{\cdot}28$ for that with fluoride ions. The reactions of the dimethyl ester were too fast to be measured at 0°. The effect of variations of the alkyl group is seen to be more marked with respect to reactions with anions than with neutral nucleophilic reagents (*J.*, 1953, 502).

The effect of change of solvent was studied by comparing the rate of reaction of di*iso*propyl phosphorochloridate with fluoride ion in dry ethanol and in 60% aqueous ethanol. In the latter, the rate of solvolysis is no longer negligible compared with the rate of reaction with fluoride ion, and special methods were required to obtain the rate of the latter reaction (cf. p. 510). It was found that the rate of the fluoride reaction in 60% aqueous

* Part I, preceding paper.

ethanol at 25° is 0·039 l. mole^{-1} sec.$^{-1}$, *i.e.*, about six times slower than in dry ethanol (0·23 l. mole^{-1} sec.$^{-1}$). Only a small salt effect was observed for a reaction with ethoxide ion: in dry ethanol at −8·5°, the rate of reaction changed from 0·0062 without added salt to 0·0076 l. mole^{-1} sec.$^{-1}$ in the presence of 0·072 mole/l. of sodium perchlorate (the initial concentration of ethoxide ions was 0·023 mole/l. in each case).

Experimental

Materials.—Absolute ethanol and dialkyl phosphorochloridates were prepared as described in Part I (*loc. cit.*). Sodium ethoxide solutions were prepared by dissolving sodium in ethanol and standardised by titration with hydrochloric acid. Potassium fluoride solutions were prepared by dissolving anhydrous potassium fluoride (obtained by heating the acid fluoride in a platinum crucible to red heat) in the desired solvent and standardised by titration with thorium nitrate solution in 50% ethanol with sodium alizarinsulphonate as indicator (Willard and Winter, *Ind. Eng. Chem. Anal.*, 1933, **5**, 7). Sodium phenoxide and sodium thiophenoxide solutions were obtained by adding phenol or thiophenol in slight excess to a solution of sodium ethoxide of the desired concentration in ethanol. The equilibrium ethoxide + phenol (thiophenol) = ethanol + phenoxide (thiophenoxide) will be almost completely to the right. The total concentration of thiophenol and thiophenoxide was determined by titration with an alcoholic solution of iodine (Klason and Carlson, *Ber.*, 1906, **39**, 739). The concentration of thiophenoxide alone was determined by adding excess of standard hydrochloric acid solution and back-titrating with sodium hydroxide (methyl-orange).

Rate Measurements.—The rate of substitution of chlorine in dialkyl phosphorochloridates by ethoxide, phenoxide, and fluoride ions was followed by electrometric titration of chloride ions in samples of the reaction mixture, as described in Part I with the following modifications:

Reaction with ethoxide. Sodium ethoxide reacts with dialkyl phosphorochloridates to form sodium chloride and a trialkyl phosphate. Since the solubility of sodium chloride in absolute ethanol at 18·5° is only about 0·01 mole/l. (de Bruyn, *Z. physikal. Chem.*, 1892, **10**, 782), a homogeneous reaction mixture was obtained by preparing solutions so dilute that the solubility product of sodium chloride was not exceeded. The reactions were carried out in a measuring flask. At definite intervals samples of 5 or 10 ml. were withdrawn and introduced quickly into 20—25 ml. of a cooled solution of 95% ethanol containing a slight excess of sulphuric acid. Chloride ion was then titrated electrometrically with silver nitrate. For the more concentrated solutions, samples of the reaction mixture were introduced into tightly stoppered test-tubes and kept for measured times in the thermostat. The contents of the tubes were then poured quickly into ethanol containing sulphuric acid, the precipitated sodium chloride on the walls of the test-tube was washed out with small amounts of ethanol (altogether 25 ml. of ethanol were used), and the chloride was determined as above.

The following example of the reaction of di*iso*propyl phosphorochloridate (initially 0·0101 mole/l.) with sodium ethoxide (0·0219 mole/l.) in absolute ethanol at 0° illustrates the determination of second-order rate constants. The reaction was carried out in a measuring flask; samples of 10 ml. were withdrawn for every titration:

Time, sec.	0	154	332	570	967	1405	1750	2270	2966	∞
0·00919N-$AgNO_3$, ml.	1·33	1·65	1·91	2·27	2·88	3·63	4·01	4·56	5·25	10·94
10^4k_2	—	109	91	90	92	101	96	95	95	—

Mean: $k_2 = 0·0096 \pm 0·0005$ l. mole^{-1} sec.$^{-1}$.

This result, together with means of those of further runs under similar conditions, gave an average value of $k_2 = 0·010_4$, which is represented in Table 1. Other rate constants were determined similarly. The rate constants were calculated by the equation $k_2 = [2·303/t(b - a)] \times \log b(a - x)/a(b - x)$ in l. mole^{-1} sec.$^{-1}$, where a and b are the initial concentrations of phosphorochloridate and ethoxide ions and x is that of chloride ions at time t. Since the rate of solvolysis of di*iso*propyl phosphorochloridate in ethanol is so much less than the rate of reaction with sodium ethoxide, the former can be neglected in calculating the rate constants.

Reaction with phenoxide. The measurement of the rate was similar to that used for the ethoxide. However, since the phenoxide reacts much more slowly, it was necessary to introduce a correction for the simultaneous solvolysis, and Moelwyn-Hughes's method was used (*Proc. Roy. Soc.*, 1949, *A*, **196**, 540). Only a few runs were carried out; these were of rather low precision, but the approximate value of $k_2 = 0·003$ l. mole^{-1} sec.$^{-1}$ was obtained.

Reaction with fluoride. The solubility of potassium chloride in absolute ethanol is 0·011 mole/l. at 25° (McIntosh, *J. Phys. Chem.*, 1903, **7**, 350) and the reaction could be carried

out homogeneously by working with solutions having a final chloride concentration lower than that value. For higher concentrations the test-tube method described above was used. An upper limit to the concentration was, however, imposed by the solubility of potassium fluoride in ethanol, *i.e.*, *ca.* 0·018 mole/l. at 20° (Germuth, *J. Franklin Inst.*, 1931, **212**, 346; Landolt–Börnstein's " Tabellen," III, 638). In view of the formation of toxic di*iso*propyl phosphorofluoridate (fluorophosphonate), pipettes were filled by slight suction with a water-pump. Samples were introduced into cold ethanol and titrated for chloride ions as above. The presence of fluoride did not interfere with the titration of chloride. The following example illustrates the determination of the rate constants :

Di*iso*propyl phosphorochloridate (initially 0·0052 mole/l.) in absolute ethanol at 25·14°. Reaction in a measuring flask; 10 ml. withdrawn for each titration.

Time, sec.	0	225	549	890	1215	1710	2140	2753	∞
0·00571N-$AgNO_3$, ml.	2·80	4·63	6·00	7·05	7·70	8·11	8·43	8·69	9·06
k_2, l. mole^{-1} sec.$^{-1}$ ...	—	0·22	0·22	0·21	0·25	0·23	0·24	0·23	—

Mean $k_2 = 0·23 \pm 0·01$ l. mole^{-1} sec.$^{-1}$.

A duplicate run (No. 81) gave a mean value of $k_2 = 0·22$ l. mole^{-1} sec.$^{-1}$.

*Isolation of di*iso*propyl phosphorofluoridate from the reaction mixture.* Since potassium fluoride is so slightly soluble in ethanol, the preparation of the ester was modified as follows. Finely ground, dry potassium fluoride (12 g.; 0·2 mole) (obtained by heating the salt in a stainless-steel pot at 200—300°, breaking it into lumps, and grinding it while still hot in a mill) and absolute ethanol (200 ml.) were placed in a flask fitted with a dropping-funnel and connected to a downward condenser. The ethanol was brought to the boil and when distillation started di*iso*propyl phosphorochloridate (19 g., 0·05 mole) was added dropwise (10 minutes). The distillation was continued until most of the ethanol was removed. The residue was neutralised with a little barium carbonate and filtered. The filtrate was distilled; it had b. p. 84—88°/26 mm. (3·5 g.) (Found: F, 10·1; P, 16·5. Calc. for $C_6H_{14}O_3PF$: F, 10·3; P, 16·9%). Saunders and Stacey (*J.*, 1948, 699) give b. p. 82—83°/21 mm.

For the reaction of di*iso*propyl phosphorochloridate with fluoride ions in 60% aqueous ethanol the simultaneous solvolysis cannot be ignored. Moelwyn-Hughes's method (*loc. cit.*) of correction could not be rigorously applied to our runs in which only the rate of production of chloride ions was followed experimentally, leaving the instantaneous value of the fluoride-ion concentration unknown. By allowing the reactions to proceed to completion and then determining both fluoride and chloride ions, a value was deduced for the rate constant of the reaction with the first ion. The rate of evolution of chloride ion is given by $dx/dt = k_2(a - x)y + k_1(a - x)$, where a = initial concentration of di*iso*propyl phosphorochloridate, x and y are the instantaneous values for the concentration of chloride and fluoride ions, k_2 the desired rate constant, and k_1 the first-order rate constant for the solvolysis reaction. Similarly, the rate of production of fluoride ions is $-dy/dt = k_1(a - x)y$, whence $-dx/dy = 1 + k_1/k_2y$. Integrating, we obtain $k_2 = [2·303k_1/(b - a - z)] \log (z/b)$, where b and z are the initial and final concentrations of fluoride ions. In one of our experiments carried in 60% aqueous ethanol at 25° (where $k_1 = 5·8 \times 10^{-4}$ sec.$^{-1}$), $a = 0·0121$ and $b = 0·0149$ mole/l. After reaction, z was found to be 0·0096 mole/l. in solution. Therefore,

$$k_2 = \frac{2·303 \times 5·8 \times 10^{-4}}{0·0149 - 0·0121 - 0·0096} \cdot \log \frac{0·0096}{0·0149} = 0·038 \text{ l. mole}^{-1} \text{ sec.}^{-1}.$$

The value of k_2 obtained above, when compared with k_1, would indicate that Moelwyn-Hughes's method (*loc. cit.*) could be applied to our initial rate constants for the reaction of di*iso*propyl phosphorochloridate with fluoride ions in 60% ethanol, with an error not exceeding 15%. The application of this method to one of our runs is illustrated below. For the reaction of di*iso*propyl phosphorochloridate (initial concentration $a = 0·035$ mole/l.) with fluoride ions (initially $b = 0·10$ mole/l.) the observed first-order (drifting) constant at 6·5 minutes was $k_1' = 32·4 \times 10^{-4}$ sec.$^{-1}$. At that time the amount of chloride ion produced was $x = 0·029$ mole/l. Applying Moelwyn-Hughes's formula, *viz.*, $k_2 = (k'_1 - k_1)y$, and assuming $y = b - x$, *i.e.*, that the amount of fluoride disappearing is equal to chloride produced, we obtain, after substituting the appropriate values, $k_2 = (32·4 - 5·8) \times 10^{-4}/0·071 = 0·039$, in reasonable agreement with the value determined above.

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103. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part III.* Reactions with Amines.*

By I. Dostrovsky and M. Halmann.

The reactions of dimethyl, diethyl, and di*iso*propyl phosphorochloridate with aliphatic primary, secondary, and tertiary amines are of second order, the rate decreasing in going from the methyl to the di*iso*propyl ester. Increase of the dielectric constant of the solvent leads to a strong acceleration. Added salts have a similar effect. The reactions with amines show the effect of steric interference on the approach of the reagent to the phosphorochloridate. The reactions are "slow" in that they possess low apparent activation energies and low Arrhenius frequency factors. A number of new dialkyl *N*-substituted phosphoramidates have been prepared.

Continuing our investigations of the reactions of dialkyl phosphorochloridates with nucleophilic reagents we have examined the action on the ester of primary, secondary, and tertiary aliphatic amines and of aniline. The studies were directed at elucidating the effect of the structures of the reagents and also solvent and salt effects. A broad survey of the reactions of dimethyl, diethyl, and di*iso*propyl phosphorochloridate with a number of amines was carried out. The reactions of the di*iso*propyl ester with a small number of amines in a variety of solvents were then studied with greater precision in order to elucidate solvent and salt effects. The solvents used included dry methanol, *n*-heptane, benzene, acetone, nitrobenzene, nitromethane, acetonitrile, and dioxan. With the exception of those with tertiary amines, the reactions of dialkyl phosphorochloridates with amines are of second order. This fact is demonstrated clearly in Table 1.

Table 1. *Rate constants for the reactions of di*iso*propyl phosphorochloridate with di-*n*-butylamine in ethanol at 25·1°.** (Second-order rate constants.)

Initl. concn. of $Cl{\cdot}PO(OPr^i)_2$, mole/l.	0·048	0·057	0·17
,, ,, amine, mole/l.	0·12	0·18	0·47
k_2, l. mole^{-1} sec.$^{-1}$	0·0055	0·0053	0·0054

* Similar results were obtained in acetone solution.

The reactions proceed according to the equation $2NHR'R'' + (RO)_2POCl = (RO)_2PO(NR'R'') + NHR'R'',HCl$, as is shown by the isolation (see p. 513) of the expected amides. Two moles of amine disappear for each mole of phosphorochloridate reacting, one mole being precipitated (in most cases) as the hydrochloride.

With triethylamine in benzene solution, di*iso*propyl phosphorochloridate reacts slowly ($k_2 = 0{\cdot}5 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$ at 0°) but only one mole of amine reacts and is precipitated as the hydrochloride. The nature of the product containing the phosphorus was not established and no olefin could be detected in the reaction mixture.

The effect of structural variations within the phosphorochloridate is illustrated in Table 2, and the effect of changes in amine structure in Table 3.

Reference to Table 2 shows that the rates of the solvolytic reactions and of those with anions and amines are affected similarly by variations in the alkyl groups of the dialkyl phosphorochloridates. This point is discussed in Part IV (following paper).

It was found that a secondary reacts much more slowly than the corresponding primary amine. Further, it is evident that branching in the α-position has a strong inhibiting effect on the rate (compare *n-*, *sec.-*, and *tert.*-butylamine), indicating the operation of steric factors. Lastly, the slowness of reaction of aniline is in keeping with its weaker basicity.

It is generally accepted that the nucleophilic power of a reagent, at least in a group of similar reagents, is closely related to its base strength. Now the latter property is usually defined with respect to the hydroxonium ion as acid, whereas in our reactions the "acid"

* Part II, preceding paper.

is the much bulkier phosphorochloridate. Brown and his school (cf. summary in *Science*, **1946**, **103**, 385) have shown that the relative base strength of a series of amines depends on the reference acid used for the comparison. When the reference acid is of small volume, the sequence of base strength approximates to that expected from the operation of the

TABLE 2. *Reactions of dialkyl phosphorochloridates with di-*n*-butylamine in dry ethanol.* (Second-order rate constants, in l. mole^{-1} sec.$^{-1}$.) *

Phosphoro-chloridate	Rate constant, k_2, at: −12·9°	0°	25°	39·6°	E_A, kcal./mole	10^{-4} PZ, l. mole^{-1} sec.$^{-1}$
Dimethyl	0·019 [a]	0·039 [a]	—	—	8	10
Diethyl	0·008 [a]	0·019 [a]	—	—	8	5
Di*iso*propyl.....	0·0007 [a]	0·0012 [a]	0·0055 [b]	0·0103 [b]	8·9	2·0

[a] Measured by conductometric method and of low precision (about ±20%). [b] Measured by titration of liberated acid and of higher precision (±2%).

* The activation energies are probably accurate to within 2 kcal., with a corresponding range for the PZ factor.

TABLE 3. *Reactions of di*iso*propyl phosphorochloridate with various amines in benzene.* (Second-order rate constants, in l. mole^{-1} sec.$^{-1}$ × 10^4.)

Amine	Method *	Temp. 25·1°	39·6°	63·8°
n-Butylamine	(*a*)	300	—	—
iso- ,, ...	(*b*)	660	—	—
sec.- ,, ...	(*b*)	—	120	—
tert.- ,, ...	(*b*)	—	2	—
Diethylamine	(*b*)	—	11	—
Di-*n*-butylamine	(*a*) (*b*)	6	11	20
Di-*sec.*- ,, ...	(*b*)	—	0·1	0·3
Aniline	(*a*)	—	0·02	—

* (*a*) By titration of liberated chloride. (*b*) By titration of liberated acid.

usual electronic effects. On the other hand, when the reference acid is bulky, the order of base strength is different and may be determined entirely by the degree of steric interference to the approach of the amine and acid. These considerations lead us to expect the sequence of base strength and nucleophilic power with respect to the chlorophosphonate to be: primary > secondary > tertiary amines, and also for variations in the alkyl group of primary or secondary amines: *n*- > *sec.*- > *tert.*-butyl. Reference to Table 3 shows that such is indeed the case. This steric factor is of, course, additional to the usual electronic factor determining the base strength. Amines which are weak with respect to hydrogen ion, through the operation of electronic effects, can only be weaker still with respect to the bulkier acid (cf. the case of aniline).

Somewhat similar results were obtained by Arnett, Muller, and Day (*J. Amer. Chem. Soc.*, 1950, **72**, 5635), who, studying the aminolysis of methyl acetate, observed that the rate for reaction with *sec.*-butylamine was 46 times slower than that with *n*-butylamine, and the reaction with *tert.*-butylamine was immeasurably slow. These values should be compared with our results, where the reactions of *sec.*- and *tert.*-butylamine with di*iso*propyl phosphorochloridate are respectively 5 and *ca.* 300 times slower than that of *n*-butylamine. The effect in the two reactions compared is in the same direction as above, but less pronounced in the phosphorus compounds.

These reactions can be described as " slow " reactions, having an Arrhenius frequency factor far lower than the calculated collision frequency. This is associated, as in other " slow " reactions, with an unduly low apparent activation energy. Inspection of Tables 2 and 3 shows that the effect of temperature is small.

In this respect the reactions are similar to Menschutkin reactions and to the reactions of benzoyl chloride with amines. The effect of the solvent is again similar to that observed in such reactions. The strong accelerating effect of solvents of high dielectric constant should be particularly noticed (cf. Table 4): *e.g.*, the change from benzene to ethanol as solvent leads to a 9-fold, and that from benzene to nitrobenzene to a 100-fold increase in

the rate. These values should be compared with the values of 11 and 35 for the corresponding effect of solvent changes in the reaction between ethyl iodide and trimethylamine (Grimm, Ruf, and Wolff, *Z. physikal. Chem.*, 1931, *B*, **13**, 301). The salt effects presented in Table 5 are also typical of such reactions.

TABLE 4. *Diisopropyl phosphorochloridate and di-*n*-butylamine: solvent effect.* ($k_2 \times 10^2$, in l. mole^{-1} sec.$^{-1}$.)

Solvent	Method	−12·9°	0°	Temp. 25·1°	39·6°	63·8°	Dielectric constant
n-Heptane	(*b*)	—	—	0·017	—	—	4·3
Benzene	(*a*) (*b*)	—	—	0·06	0·11	0·20	2·28
Ethanol	(*a*)	0·07	0·12	0·55	1·2	—	25·8
Dioxan	(*a*)	—	—	0·8	—	—	2·28
Acetone	(*a*)	—	0·8	2·5	—	—	21·4
Nitromethane	(*b*)	—	—	4·0	—	—	39·4
Nitrobenzene	(*a*)	—	—	6·0	—	—	36·1
Acetonitrile	(*a*)	—	—	7·5	—	—	38·8

(*a*) By titration of liberated chloride. (*b*) By titration of liberated acid.

TABLE 5. *The reaction of diisopropyl phosphorochloridate with di-*n*-butylamine at 25° in the presence of added substances.*

Solvent	Amine, mole/l.	Ester, mole/l.	Added substance	k_2, l. mole^{-1} sec.$^{-1}$
Benzene	0·083	0·016	—	0·0005
Benzene	0·044	0·0089	NEt_3, 0·18N	0·0005
Ethanol	0·12	0·048	—	0·0055
Ethanol	0·10	0·042	$(Pr^iO)_2PO(NBu^n_2)$, 0·04M	0·008
Ethanol	0·12	0·040	NH_2Bu_2Cl, 0·12M	0·015
Ethanol	0·047	0·020	$NaClO_4$, 0·2M	0·02
Ethanol	0·10	0·020	NH_4NO_3, 0·2M	0·07

EXPERIMENTAL

(M. p.s are uncorrected.)

Materials.—Phosphorochloridates were prepared as described in Part I (*loc. cit.*). Technical heptane was stirred for 3 days with distilled chlorosulphonic acid, washed successively with pure sulphuric acid, aqueous sodium hydroxide, and water, dried ($CaCl_2$), and distilled twice through a Vigreux column. It showed no appreciable absorption in the ultra-violet spectrum down to 2400 Å. Benzene of technical grade was distilled, the first portion being discarded. Ethanol was dried by the ethyl phthalate method (Manske, *J. Amer. Chem. Soc.*, **1931**, **53**, 1106). Technical dioxan was refluxed with sodium and fractionated through a 30-cm. vacuum-jacketed column packed with Fenske glass helices. (This column was used also in all fractionations of materials described in this section.) Acetone (ACS grade) was distilled before use. Nitromethane (Eastman Kodak Co.) was distilled from phosphoric anhydride. Aniline (C. P., Baker's "Analysed") was used without further purification. Diethylamine (Sharples) was dried (KOH) and fractionated.

n-, *iso-*, and *sec.*-Butylamine, di-*n*-butylamine, di-*sec.*-butylamine (Eastman Kodak) were dried (KOH) and fractionated. The last had b. p. 131°; Mailhe (*Compt. rend.*, 1905, **33**, 965) reported b. p. 132°/758 mm.

tert.-Butylamine, prepared according to Pearson, Baxter, and Carter (*J. Amer. Chem. Soc.*, 1948, **70**, 2290; *Org. Synth.*, **29**, 21), had b. p. 44—45°.

Preparation of Esters of N-*Substituted Phosphoramidic Acids* NR′R″·PO(OR)$_2$.—(a) *Dimethyl* NN-*di-*n*-butylphosphoramidate* (R = Me, R′ = R″ = Bu). Dimethyl phosphorochloridate (2·9 g.) and di-*n*-butylamine (5·2 g.), dissolved in dry ether (50 ml.), were left in a stoppered flask at room temperature for 2 days, the precipitate was filtered off, and the filtrate distilled, yielding the *ester* as a colourless oil, b. p. 157—159°/41 mm., n_D^{25} 1·4327 (2·5 g., 53%) (Found: C, 49·4; H, 10·1; N, 6·0; P, 12·8. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9; P, 13·1%).

(b) The corresponding *diethyl* ester was prepared analogously (58% yield), b. p. 104—106°/1 mm., n_D^{25} 1·4299 (Found: C, 54·5; H, 10·9; N, 5·2; P, 12·0. $C_{12}H_{28}O_3NP$ requires C, 54·5; H, 10·6; N, 5·3; P, 11·7%). Di-*n*-butylamine hydrochloride was isolated in 58% yield.

(c) *Diisopropyl* NN-*diethylphosphoramidate* (R = Pr^i, R′ = R″ = Et). Di*iso*propyl phosphorochloridate (2·06 g.) and diethylamine (2·3 ml.), in benzene (30 ml.), were kept for 2 days. A precipitate of diethylamine hydrochloride was filtered off (1·1 g., 98%), m. p. 222—225°. The filtrate was fractionated to yield the *ester* as an oil (2·1 g.), 86%, b. p. 52—61°/0·1 mm. (Found: C, 51·2; H, 10·5; N, 5·6. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9%).

(d) *Diisopropyl* N-n-*butylphosphoramidate* (R = Pr^i, R′ = H, R″ = Bu^n). Di*iso*propyl phosphorochloridate (3·0 g.) and *n*-butylamine (3 ml.) in benzene (20 ml.) similarly gave *n*-butylamine hydrochloride, m. p. 210° (Found: Cl, 31·4. Calc. for $C_4H_{12}NCl$: Cl, 32·4%), and the *ester* as an oil (1·1 g., 27%), b. p. 99—101°/0·5 mm., n_D^{25} 1·4239 (Found: C, 51·1; H, 10·2; N, 6·9; P, 12·6. $C_{10}H_{24}O_3NP$ requires C, 50·6; H, 10·1; N, 5·9; P, 13·1%).

(e) *Diisopropyl* N-iso*butylphosphoramidate* was similarly prepared, but cooling with ice was necessary at first; it was an oil (63% yield), b. p. 103·5—104°/1·5 mm. (Found: C, 51·4; H, 10·9; N, 5·9%). *iso*Butylamine hydrochloride, m. p. 167°, was also obtained (83%).

(f) The sec.-*butyl* analogue was similarly prepared. Addition of light petroleum to the reaction mixture precipitated *sec.*-butylamine hydrochloride (90%), m. p. 144—145°, and the filtrate afforded the ester (75% yield), b. p. 101°/2 mm., m. p. 20—30° (Found: C, 50·9; H, 10·8; N, 5·8%).

(g) Analogous methods afforded *tert.*-butylamine hydrochloride, m. p. 275—282° (91% yield), and *diisopropyl* tert.-*butylaminophosphoramidate*, b. p. 107—112°/3 mm., m. p. 60—62° (83% yield) (Found: C, 50·6; H, 10·5; N, 5·9%).

(h) *Diisopropyl* NN-*di*-n-*butylphosphoramidate* (R = Pr^i, R′ = R″ = Bu^n), a colourless oil, had b. p. 110—112°/2 mm., n_D^{25} 1·4272 (yield 27%) (Found: C, 56·8; H, 11·1; N, 5·1; P, 10·6. $C_{14}H_{32}O_3NP$ requires C, 57·3; H, 10·9; N, 4·8; P, 10·6%); and di-*n*-butylamine hydrochloride (98% yield) (Found: Cl, 20·7. Calc. for $C_8H_{20}NCl$: Cl, 21·5%) was also obtained.

(i) *Diisopropyl* NN-*di*-sec.-*butylphosphoramidate*. Di*iso*propyl phosphorochloridate (2·86 g.) and di-*sec.*-butylamine (4·0 g.), in acetonitrile (16 ml.), were kept for 2 days at 65°, then added to water (50 ml.) and extracted with light petroleum (50 ml.). After being dried (Na_2SO_4) and distilled, the *ester* was obtained as a colourless oil, b. p. 84—88°/1·5 mm. (0·5 g., 12%) (Found: C, 56·9; H, 10·6; N, 4·4%). Attempts to prepare this ester in benzene solution failed, because of the slowness of reaction. The di-*sec.*-butylamine hydrochloride produced was easily soluble in benzene, but could be precipitated with light petroleum (Found: Cl, 21·0. Calc. for $C_8H_{20}NCl$: Cl, 21·4%). Its m. p. after drying *in vacuo* at 60° was 115—120°, scarcely changed by dissolution in ethyl methyl ketone and precipitation with light petroleum. A sample prepared by bubbling hydrogen chloride through a light petroleum solution of the base also melted at 117—119°. Mailhe (*Compt. rend.*, 1905, **33**, 965) reported the salt to be very hygroscopic and did not give a m. p.

(j) *Diisopropyl* N-*phenylphosphoramidate*. Di-*n*-butylamine (16·8 ml.) was added slowly to diphenyl phosphorochloridate (14·2 g.) in dry ether (50 ml.) cooled by tap water. After 5 hours the precipitate was filtered off, and the filtrate, after being washed with water and dried (Na_2SO_4), afforded the *ester* as a slightly viscous oil (12·4 g., 69%), b. p. 170—173°/0·5 mm., n_D^{25} 1·5173 (Found: C, 66·2; H, 7·9; N, 4·1; P, 8·6. $C_{20}H_{28}O_3NP$ requires C, 66·4; H, 7·8; N, 3·9; P, 8·6%).

Kinetic Measurements.—The reactions of amines with phosphorochloridates were followed by finding the rates of formation of chloride ion (*a*) by titration and (*b*) conductometrically, and (*c*) the rate of disappearance of free amine acidimetrically.

(a) *Titration method.* Samples (3 or 5 ml.) of the reaction mixture were run into cold 95% ethanol containing sulphuric acid in slight excess over that required to neutralize the free amine, and the chloride ion titrated with silver nitrate electrometrically (Part I). Second-order rate constants were calculated from the formula $k_2 = [2{\cdot}303/t(b - 2a)] \log a(b - 2x)/b(a - x)$, where a and b are the initial concentrations of phosphorochloridate and amine, and x is the concentration of chloride ions at time t (see equation, p. 511).

The rate constants obtained in this way showed a marked upward drift. This is not surprising in view of the marked salt effect (see Table 5). The rate constants were extrapolated to zero reaction and are thus the values for solutions with negligible ionic strength.

The method as described is suitable for reactions in solvents in which the amine hydrochloride is soluble, such as ethanol, acetone (0·01M-solutions), and acetontrile. Di-*sec.*-butylamine hydrochloride was soluble in benzene. For other solvents or amines, where amine hydrochlorides were sparingly soluble, samples of the reaction mixture were pipetted into glass-stoppered tubes (for fast reactions) or sealed in ampoules and kept for given periods of

time in the thermostats. The contents were then washed out into cold acidic ethanol and titrated. An example is given herewith :

Reaction of diisopropyl phosphorochloridate (0·0464M) *with di-n-butylamine* (0·141M) *in absolute ethanol at* 0·0°.

t, sec.	0	293	675	1093	1860	3198	10,520	11,450	∞
0·00966N-$AgNO_3$, ml.	1·69	2·58	4·00	5·38	7·80	10·41	18·49	19·10	23·52
$k_2 \times 10^4$, l. mole^{-1} sec.$^{-1}$	—	10·1	11·9	12·7	13·6	13·4	13·8	14·2	—

(b) *Conductometric method.* This method was used only for reactions in ethanol to obtain approximate rate constants for fast reactions at low temperatures. The technique was as described in Part I (*J.*, 1953, 507). The conductivity of the mixture is very sensitive to traces of water, an effect which could only be overcome by considerably more elaborate technique than was used. In calculating the rate constants it was assumed that the conductivity was proportional to the concentration of amine hydrochloride. This assumption was checked by constructing calibration curves and found to be sufficiently accurate in the range of concentration used. Second-order rate constants were calculated from the observed values of the resistance by substitution in the equation for the second-order rate constant (above) the value $x = a(R/R_t)$, where R and R_t are the values of the resistance of the cell at the end of the run and at time t, respectively. When log $2(b/2aR - 1/R_t)/(1/R - 1/R_t)$ is plotted against time a straight line is obtained, the slope of which is equal to $k_2(b - 2a)/2{\cdot}303$. An example is given below.

Reaction of diisopropyl phosphorochloridate (0·00914M) *with di-n-butylamine* (0·0985M) *in dry ethanol at* 0·23°.

Time, min.	0	5	10	20	38	40	51	65	∞
Resistance, ohms	18,000	12,560	9870	7170	6020	4980	4380	3870	2035·3

From the slope of the line taken between 10 minutes and infinity the value of 0·0017 l. mole^{-1} sec.$^{-1}$ was obtained for k_2.

(c) *Acidimetric method.* The rate of reaction of amine could be observed acidimetrically. Samples of the reaction mixture (3 or 5 ml.) were run into a mixture of 20 ml. of acetone and 5 ml. of a standard solution of perchloric acid in dioxan. The amount of perchloric acid was calculated to be slightly in excess over the initial amount of the amine in the sample. The excess of acid was back-titrated with a standard solution of triethylamine in toluene, lacmoid being used as indicator. The presence of ethanol up to about 15% did not interfere. *s*-Diphenylguanidine (recrystallized three times from toluene), m. p. 147—148°, served as primary standard (Carlton, *J. Amer. Chem. Soc.*, 1922, **44**, 1469). Triethylamine was found not to react with dialkyl phosphorochloridates under the conditions of this titration.

This titration method was found to be the most convenient, since it could be easily used for reactions having a half-life as short as 1 minute at room temperature, and moreover was not disturbed by precipitation of amine hydrochloride. Two examples follow.

Reaction of diisopropyl phosphorochloridate (0·0412M) *with* isobutylamine (0·194M) *in benzene at* 25·1°.

t, sec.	0	27	55	82	119	
NH_2Bu^i, mole/l.	0·165	0·152	0·142	0·135	0·129	
k_2, l. mole^{-1} sec.$^{-1}$	—	0·063	0·066	0·067	0·067	Mean 0·066

Reaction of diisopropyl phosphorochloridate (0·0550M) *with di-n-butylamine* (0·1772M) *in absolute ethanol at* 0°.

t, sec.	0	330	1410	2275	2732	3615	5310	7550
$NHBu_2$, mole/l.	0·1677	0·1620	0·1435	0·1340	0·1220	0·1193	0·1097	0·0986
10^4k_2, l. mole^{-1} sec.$^{-1}$	—	10·9	12·8	12·2	12·8	13·2	12·4	12·7

Mean $k_2 = 0{\cdot}00124 \pm 0{\cdot}0001$ l. mole^{-1} sec.$^{-1}$.

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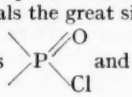
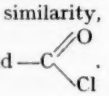
104. *Kinetic Studies in the Phosphinyl Chloride and Phosphorochloridate Series. Part IV.* General Discussion.*

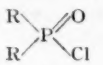
By I. Dostrovsky and M. Halmann.

The results of the kinetic investigations reported in the three preceding papers are critically analysed, and the possible mechanism discussed. Special attention is paid to the possible existence in these reactions of a " transition complex " possessing an expanded valency shell of the phosphorus atom. No evidence could be obtained for any great stability of such a complex. The reactions studied in the previous papers are thus assumed to be simple bimolecular displacements similar to those observed with the analogous carbon compounds. The comparison of the reactions of the phosphorochloridates and phosphinyl chlorides with their carbon analogues reveals the great similarity, both qualitatively and quantitatively, of the groupings  and  .

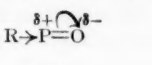
The ability of elements of the second and higher rows of the Periodic Table to use more than four orbitals in bond formation has been invoked to explain the marked differences in the rates of hydrolysis and alcoholysis of their halides as compared with those of carbon (cf. Sidgwick, " Electronic Theory of Valency," Oxford Univ. Press; *J.*, 1924, **125**, 2672). This view assumes the formation of a relatively stable " transition complex " using an extra bonding orbital, which then undergoes decomposition by a unimolecular process. In this process the requirement of simultaneous bond breaking and bond formation, essential in the S_N2 type of mechanism, is waived, so that reaction is facilitated. The experiments described in Parts I—III were undertaken in order to test the applicability of this view to the reactions of the phosphorohalidates and related compounds.

With the possible exception of the solvolysis in formic acid and the reaction with tertiary amines, the reactions of the phosphorochloridates and phosphinyl chlorides are simple substitutions at the phosphorus atom. The kinetic analysis of these reactions provides no evidence for an S_N1 type of reaction and leads to the conclusion that the solvolyses and the second-order reactions with strong nucleophilic reagents proceed by the same mechanism. We now examine the possible routes of these reactions in the light of our evidence.

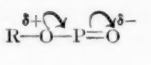
The effect of structural changes in the phosphorochloridates and phosphinyl chlorides may be understood by considering the possible interaction of the groups R with the oxygen atom in the compound (I). On account of the electronegativity difference between oxygen



(I)



(II)



(III)

and phosphorus, and between chlorine and phosphorus, the phosphorus atom will carry a small positive charge and be the electrophilic centre of the molecule. Any electron release from the group R will weaken this centre. Such electron release may be caused by inductive effect in the group R, or by an electromeric effect if the group R contains unshared p-electron or π-electrons. These effects are represented in (II) and (III). Using the well-established principles governing these effects, we can arrange the groups in order of their electron release to the P atom, *viz.*: Me < Ph; Me < MeO < EtO < PrO. Reference to Table I of Part I (*J.*, 1953, 502) and Tables 2 and 3 of Part III (*loc. cit.*) shows that the rates of reaction decrease with electron accession to the phosphorus atom according to the same sequence. Thus a change from R = Me to R = OMe [in $Cl{\cdot}PMe_2O$ and $Cl{\cdot}P(OMe)_2O$] causes a 300-fold decrease in the rate of solvolysis in absolute ethanol. Similarly, a change from R = OMe to R = OPr^i causes a 5-fold decrease in the rate of solvolysis (dimethyl and di*iso*propyl phosphorochloridates) and a 3-fold decrease in the rate of reaction with di-*n*-butylamine. The effect of variation in structure on the

* Part III, preceding paper.

reactions with negative ions is much greater (cf. Part II, *J.*, 1953, 508) : the rate of reaction of diethyl phosphorochloridate with ethoxide ion is some 26 times that of the di*iso*propyl ester, while the rate of reaction of the first ester with fluoride ions is some 9 times that of the second.

The way in which the reaction rates depend upon the electron density on the phosphorus atom and the greater sensitivity of the rate of reaction with negative ions to changes in this density show clearly that the rate-controlling step involves the approach of the nucleophilic reagent to this atom (cf. Hinshelwood, Laidler, and Timm, *J.*, 1938, 848).

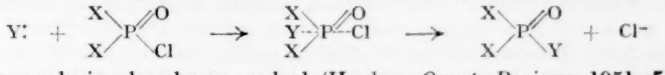
The rates of solvolysis of the esters $Cl{\cdot}PO(OR)_2$ in dry ethanol vary with R thus : $CH_2Ph > Me > Ph$, although the differences are not large. The first inequality accords with the reduced hyperconjugation of the methylene hydrogen atoms; and the second with the greater participation of the phenyl group in the electromeric effect. The situation is analogous to that in the relative strengths of *p*-substituted benzoic acids (cf. Dippy, *Chem. Reviews*, 1939, **25**, 151).

Our results are in accordance with Toy's observations (*J. Amer. Chem. Soc.*, 1948, **70**, 3882; 1950, **72**, 2065), and those by Kosolapoff and Watson (*ibid.*, 1951, **73**, 4101, 5466), that the hydrolysis of tetra-alkyl pyrophosphates is much slower than that of the corresponding anhydrides of dialkylphosphinic acid.

The view that the rate-determining step involves the approach of the reagent is supported further by the effect of structural variation of the amines in their reactions with phosphorochloridates (cf. Part III, Table 3). We have seen that the rate of sequence for various amines is in keeping with their base strength with respect to bulky reference acids. Since the base strength thus defined is determined by steric interaction between amine and acid, we conclude that in the reaction with di*iso*propyl phosphorochloidate the approach of the reagent is involved in the rate-determining step, and the reaction is then subject to steric hindrance operating between the amine and the ester. Similar reasons account for the extreme slowness of the solvolysis in *tert.*-butyl alcohol (cf. Part I, *J.*, 1953, 503).

The magnitude and direction of solvent effects give information regarding the state of electrical charge in the transition state relative to that in the reagents. Ionising solvents exert an accelerating effect in the solvolytic reactions and on the reactions with amines (cf. *J.*, 1953, pp. 503, 513). Thus, in the solvolysis of di*iso*propyl phosphorochloridate, a change from absolute ethanol to 60% aqueous ethanol increases the rate 9·4 times (Table 3, *ibid.*, p. 503), and in its reaction with di-*n*-butylamine a change from benzene to nitrobenzene causes a 100-fold increase in rate (cf. Table 4, *ibid.*, p. 513). These facts indicate that the transition state carries a higher charge than the reactants. Similarly, in the reaction of di*iso*propyl phosphorochloridate with fluoride ions, a change from absolute to 60% ethanol leads to a 6-fold decrease in rate (cf. *ibid.*, p. 508), indicating that the initial negative charge of the fluoride ion has been dispersed in the transition state (cf. Hughes, *Trans. Faraday Soc.*, 1941, **37**, 604). The observed salt effects (*ibid.*, pp. 504, 509, 513) are also consistent with these conclusions.

From the fact that *iso*propyl phosphorofluoridate reacts slower than its chlorine analogue and that the corresponding iodide reacts faster (McCombie, Saunders, and Stacey, *J.*, 1945, 380, 921), one can conclude that the bond between the halogen and the phosphorus atom is also involved in the transition state. Taking all these facts together, we can write for the reactions between the phosphorochloridates and nucleophilic reagents the usual bimolecular scheme of reaction with bond-making influences predominating :



A similar conclusion has been reached (Hughes, *Quart. Reviews*, 1951, **5**, 268) with respect to the mechanisms of solvolysis of triphenylsilyl fluoride. In cases where the reagent Y is a neutral molecule carrying a hydrogen atom, *e.g.*, water, alcohols, secondary and primary amines, the question may arise whether the elimination of the proton is involved in any rate-determining stage of the reaction. An attempt to answer this question was made by comparing the rates of solvolysis in D_2O and in ordinary water (Table 3, *J.*, 1953, 503), but the slightly slower rate in D_2O could be accounted for by the slightly different solvent

properties. A further test was carried out by observing the rates of the reaction of di*iso*propyl phosphorochloridate with di-*n*-butylamine in the presence of added triethylamine. Here also no significant effect of the added base was noted. Had proton removal been involved in a rate-determining step, considerable effects should have been observed in both the experiments described above. We therefore conclude that in solvolyses and in reactions with primary and secondary amines, the proton of the reagent is eliminated in a fast step following the rate-controlling bimolecular displacement of the halogen atom.

There is only little support for the " addition complex " theory in the evidence presented in these papers. The reactions could still be presented by the following sequence, although somewhat less satisfactorily :

$$Y + PX \underset{k_1}{\overset{k_2}{\rightleftharpoons}} YPX \xrightarrow{k_3} YP + X^-$$

whence $-d[PX]/dt = k_2k_3[Y][PX]/(k_1 + k_3)$. Now, if $k_1 \ll k_3$ the reaction reduces to the normal bimolecular reaction discussed above. However, if $k_3 \ll k_1$, the reaction can be written $-d[PX]/dt = Kk_3[Y][PX]$, where $K = k_2/k_1$.

Now, increasing electron accession to the phosphorus atom will reduce the value of K and increase k_3, so the resulting effect on the reaction will depend on the relative magnitude of these effects and in any case will be reduced by partial cancellation. In order to account for the observed direction of the effect, it is necessary to assume that the effect on K will predominate. It is impossible to give a definite answer to this point. However, the apparently reasonable magnitude of the retardation effect appears to favour a straightforward bimolecular reaction. Further doubt on the validity of the " addition complex " mechanism has been cast by Sommer and his co-workers (*J. Amer. Chem. Soc.*, 1951, **73**, 5130). It appears therefore that the mechanisms of the reactions of phosphorochloridates and phosphinyl chlorides are identical with those of analogous carbon compounds, with no new effects due to the position of the phosphorus atom in the periodic table.

Having established the similarity of mechanisms of phosphorus and carbon compounds, we proceed to compare analogous compounds in greater detail. Perhaps the most surprising result of such a comparison is the great similarity of the groups >PCl:O and —CCl:O, not only in the relative effect of changes in reaction variables on the rate of reaction, but also in the absolute values of the rate constants of the two series of compounds. Phosphorochloridates $Cl{\cdot}PO(OR)_2$ may be regarded as the analogues of chloroformates ($Cl{\cdot}CO_2R$) and the phosphinyl chlorides ($Cl{\cdot}PR_2O$) as the analogues of carboxylic acid chlorides (R·COCl). The rates of methanolysis for a number of alkyl chloroformates (Leimu, *Ber.*, 1937, **70**, 1940) are given in Table 1 together with our results for the ethanolysis of the analogous phosphorochloridates.

TABLE 1. *Kinetics of the solvolysis of alkyl chloroformates and dialkyl phosphorochloridates at 25°.*

	Chloroformates [a]			Phosphorochloridates [b]		
	$k \times 10^4$, sec.$^{-1}$	E_A, kcal./mole	$10^{-6}PZ$, sec.$^{-1}$	$k_1 \times 10^4$, sec.$^{-1}$	E_A, kcal./mole	$10^{-6}PZ$, sec.$^{-1}$
Me	1·64	15·5	4·1	5·3	12·0	0·25
Et	0·90	15·8	3·7	1·7	13·4	1·2
Pr^i	0·41	16·3	4·1	0·61	12·8	0·16

[a] Leimu (*loc. cit.*), in methanol. [b] Calc. from authors' results (*J.*, 1953, 502).

It is evident that the effect of substituents on the rates of reaction is in the same direction in the two series and only slightly more pronounced for the phosphorus compounds. It is seen that, after allowance for the difference in media, the rates of solvolysis of the phosphorus compounds are only some 4—16 times greater than those of the analogous carbon compounds. A direct comparison can be made in the case of the *iso*propyl compound where the rate of methanolysis of the phosphorochloridate is exactly 4 times that of the chloroformate (cf. *J.*, 1953, 503).

The rates of solvolysis of acetyl and benzoyl chlorides have been measured by Norris (*J. Amer. Chem. Soc.*, 1935, **57**, 1416) and by Branch and Nixon (*ibid.*, 1936, **58**, 492, 2499), whose results are compared with those for the analogous phosphinyl chlorides, *viz.*, dimethyl-

and diphenyl-phosphinyl chlorides, in Table 2. Examination of these data indicates that in these series, the effect of substituents is considerably greater in the carbon compounds. Further, a direct comparison in the same solvent between benzoyl chloride and diphenylphosphinyl chloride indicates that the latter undergoes ethanolysis some 23 times faster

TABLE 2. *Comparison of rates of solvolysis of phosphinyl chlorides with those of acetyl and benzoyl chlorides at* −8·5°.

	10^4k_1	E_A, kcal./mole		10^4k_1	E_A, kcal./mole
Acetyl chloride [a] ...	7·6	14·4	Dimethylphosphinyl chloride [c]	60·0	—
Benzoyl chloride [a] ...	0·075	12·5	Diphenylphosphinyl chloride [c]	6·8	11·0
Benzoyl chloride [b] ...	0·29	15·5			

[a] Calc. from results of Branch and Hixon (*loc. cit.*) for 40% ethanol–60% ether as solvent. [b] Calc. from results of Morris (*loc. cit.*) for ethanol as solvent. [c] Calc. from authors' results (*J.*, 1953, 503).

(at −8·5°). This factor is again similar to that obtained in the comparison of phosphorochloridates and chloroformates. It should be noted that as a consequence of the considerable difference in activation energies, the relative rates presented here depend somewhat upon the temperature at which the comparison is made.

The close analogy of the groupings >POCl and —COCl lends further support to the formulation using a double bond between the phosphorus and the oxygen atom and not to that using a " co-ordinate link " or " semipolar bond," still commonly employed. In these compounds the phosphorus atom utilizes a 3*d* orbital for its bonds, as it does in PCl_5, PBr_5 and the oxyhalides, and in agreement with the observed P–O bond lengths in the phosphate group and oxyhalides (cf. Pauling, " The Nature of the Chemical Bond," Cornell Univ. Press, 1944, pp. 84, 244).

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105. *Interfaces between Aqueous Liquids.*

By L. SAUNDERS.

Interfaces formed when normally miscible, aqueous liquids flow together through a common channel have been studied optically. The apparatus has been so designed that it can be used to study diffusion processes in clear liquids by the Gouy interference method or it can be used to photograph an interface directly when there is turbidity at the boundary.

Interfaces formed between some colloid sols of biological interest have been examined in order to provide a background for more detailed physicochemical work with materials of better-defined constitution.

Very stable interfaces have been obtained with lecithin sols and this effect is considered to be due to the spreading of a film of fatty acid at the boundary. The possibility of forming a mixed lecithin–protein film at the boundary between two aqueous liquids has been investigated and there is some evidence that such a film, which would be a very useful model for the study of biological adsorption, can be produced.

LANGMUIR and WAUGH (*J. Gen. Physiol.*, 1938, **21**, 745) wrote: " For many biological purposes it would be desirable to produce a membrane of one or two layers of protein between two aqueous phases. Such a membrane would probably have some of the properties of a cell membrane." The study of the adsorption of biologically active compounds at stable or metastable interfaces formed between two aqueous liquids should be of considerable interest, since these interfaces will have a closer resemblance to natural cell membranes than the models hitherto used for this type of work, *e.g.*, protein or lipid films spread at air–water or oil–water interfaces.

The main problem to be solved is the production of stable surfaces of separation of two aqueous liquids, in an apparatus in which the electrical and optical properties of the surface can be studied. Langmuir and Waugh attempted to achieve this by mechanically transferring films of protein, formed at air–water or oil–water interfaces, into water so as to form membranes separating two aqueous columns. This technique was not very successful; pure protein films broke up on immersion but they were considerably strengthened by incorporation of lecithin. It would seem to be more profitable to produce stable films by the interaction of two aqueous liquids at a sharp boundary temporarily formed between them.

The work reported here describes some experiments carried out with an apparatus constructed for the optical study of interfaces formed between normally miscible liquids. The production of sharp boundaries between such liquids can be effected by several methods which have been developed in connection with electrophoretic and diffusion studies of colloid sols. The three principal techniques are: (1) sliding a section of a tube containing one liquid over a stationary section containing the other (Tiselius, *Trans. Faraday Soc.*, 1937, **33**, 524; Neurath, *Science*, 1941, **93**, 431); (2) withdrawing a plate separating two liquids (Claesson modification of the Lamm cell, *Nature*, 1946, **158**, 834); (3) causing the liquids to flow together through a horizontal channel (Coulson, Cox, Ogston, and Philpot, *Proc. Roy. Soc.*, 1948, *A*, **192**, 382). Of these, the first two methods do not produce very sharp boundaries, and the third seemed preferable.

The recently revived Gouy interference method for studying diffusion (Longsworth, *J. Amer. Chem. Soc.*, 1947, **69**, 2510; Coulson *et al.*, *loc. cit.*) provides a sensitive method for studying changes at the sharp boundaries, soon after their formation.

Experimental

The apparatus used (Fig. 1) was modelled on that described by Coulson *et al.* (*loc. cit.*) and by Gosting, Hanson, Kegeles, and Morris (*Rev. Sci. Instr.*, 1949, **20**, 209). It consists of a 2-m. optical bench mounted on a steel beam supported by concrete pillars embedded in the earth beneath a basement laboratory floor. A light source (*A*, Fig. 1) consists of a mercury-vapour lamp cooled by a water jacket and fitted with appropriate filters to isolate the green line (5461 Å); the light from this is condensed on to a horizontal spectrometer slit (*B*) set at 5-μ aperture. A precision camera lens (*C*), of 13·5-cm. focal length, focuses an image of the slit through the thermostat (*D*) containing the cell on to a camera plate (*E*) at the far end of the bench. The thermostat is fitted with circular, optically flat ($\lambda/2$) windows, set accurately perpendicular to the optic axis of the bench (to within $\frac{1}{3}'$ of arc); it is supplied with constant-temperature water from a larger tank, the connections between them being so arranged as to avoid transmitting vibration to the bench.

Gosting *et al.* (*loc. cit.*) use a sliding-section type of cell in which the boundary is sharpened after formation by drawing the liquids off together through a pipette whose tip is placed at the boundary; Coulson *et al.* (*loc. cit.*) describe a Perspex cell fitted with a channel at the level of the boundary and optically flat glass windows. This fitted-channel type of cell seemed most suitable for this work, but since the use of Perspex very much restricts the temperature range in which it can be used, an all-glass cell has been constructed, Araldite cement being used to join the plate-glass pieces. Two 2 × 2 cm. windows were half wave-length optical flats, but the remainder of the cell was not of optical quality. This cell has now been replaced by an all-glass one (Fig. 2) constructed by Hilger and Watts Ltd. (The author is indebted to Mr. H. W. Yates for help in designing this cell.) The great advantage of this cell is that the optically important, lower section (*A*) consists entirely of adhering glass pieces; it contains no cement and the faces are very accurately set parallel to one another and are polished flat to a half wave-length. The upper part of the cell (*B*) consists of plate-glass pieces joined together by Araldite cement. The upper part is joined to the lower section by a cold-setting cement. The two aqueous liquids are placed on either side of the central glass partition (*C*) and the boundary between them is formed by drawing them out together through the channel (*D*); this is of 50-μ width and is set accurately perpendicular to the sides of the cell. The channel was formed by grinding out two blocks of glass which were subsequently made to adhere together. The tube (*E*) through which the liquids are withdrawn is cemented into the block of glass.

The cell is put on a platform in the thermostat so that the boundary is formed in the optic axis of the bench; this axis is adjusted to be accurately horizontal by ensuring that the image of

FIG. 1. *Diffusion apparatus.*

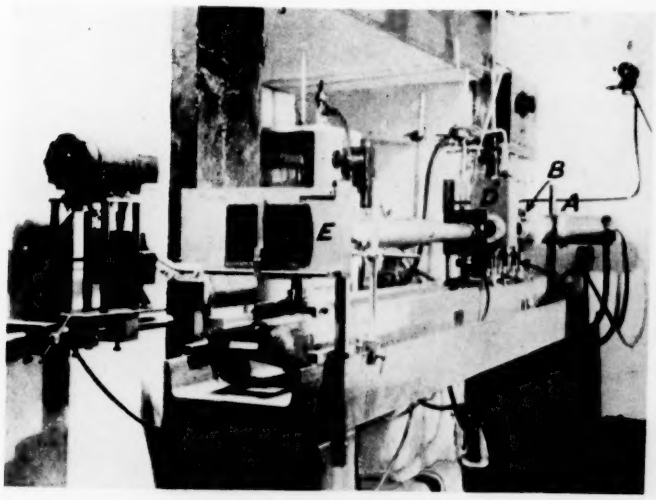
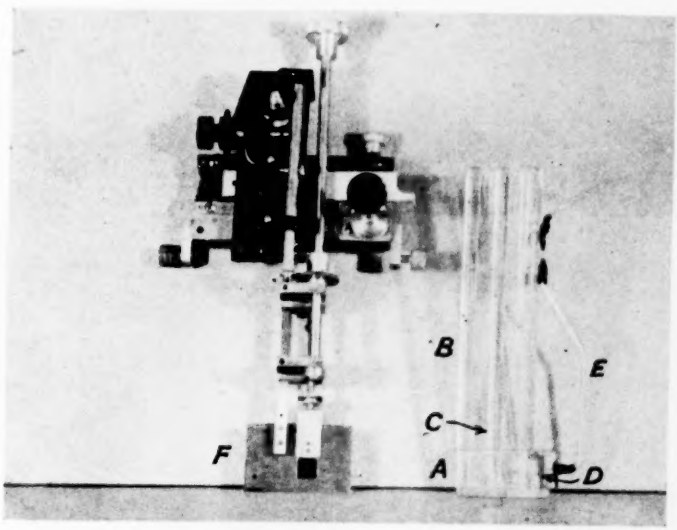
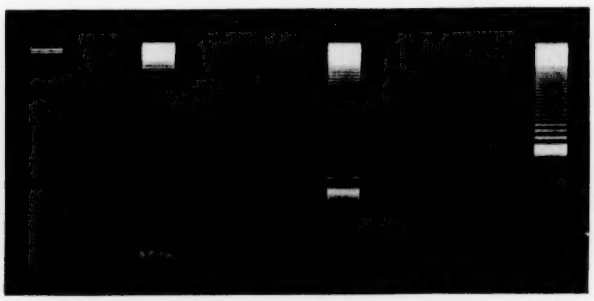


FIG. 2. *Stops and cell.*



[*To face p.* 520

FIG. 3. *Reference and Gouy patterns (glycine). Intensity minima are dark.*



t = 300 600 1200 *sec.*

FIG. 4. *Lecithin sol (dark)/water (light) interfaces, showing the outflow channel of the cell as a reference point.*

A. *While flowing.*

B. 2 *Hrs. after flow had stopped.*

C. 20 *Hrs. later.*

D. *Effect of tetradecylpyridinium bromide.*

the slit at the photographic plate is exactly the same height above the bench as the slit itself. After the flow of liquids through the cell channel has been stopped, the boundary normally spreads by diffusion and the refractive-index gradients produced cause a set of interference fringes to appear at the photographic plate, below the normal slit image. As diffusion proceeds, this Gouy pattern closes up towards the undeviated slit image, and by photographing it at different times and measuring the displacements of the intensity minima below the optic axis, the diffusion process can be quantitatively followed. The full theory of the interpretation of the patterns to yield values of diffusion coefficients is given by Kegeles and Gosting (*J. Amer. Chem. Soc.*, 1947, **69**, 2516). In this work the patterns have been measured to within a few microns, by means of a Cambridge measuring machine. A vertical slit placed immediately in front of the photographic plate enables a series of patterns to be recorded on a single plate. Normally ten seconds' exposure sufficed to give clear records of the patterns.

On the photographic plate side of the cell, fitting close up against the cell window, a set of stops is mounted (*F*, Fig. 2*a*) and these can be moved horizontally and vertically, from above the thermostat. The main aperture is 10 × 10 mm. and has serrated edges at top and bottom to break up the Fraunhofer patterns, which otherwise interfere with the Gouy pattern near the undeviated slit image; this aperture is centred on the boundary in the cell. To one side of the main aperture there are a pair of 1 × 1 mm. apertures arranged so that one is vertically above the

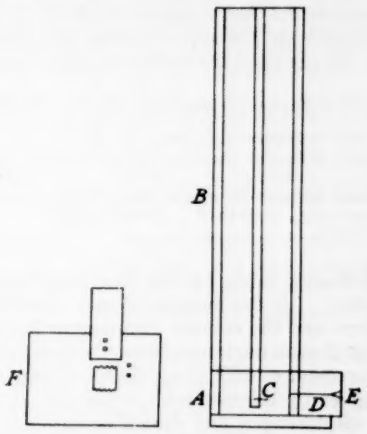


FIG. 2*a*. *Diagrams of stops and cell.*

other with a distance of about 3 mm. between them. These pass light which goes only through the glass block containing the cell channel and not through the liquids in the cell; the light from those two stops is displaced upwards by an inclined, optically flat glass plate, so producing a double slit interference pattern on the photographic plate, above the undeviated slit image; this serves as a reference trace to locate the optic axis of the apparatus, and all measurements of the patterns are referred to this trace. A similar pair of double stops can be lowered in front of the main aperture, by means of a screw.

To carry out a measurement of a diffusion coefficient, a photograph is first taken of the undeviated slit image and the reference trace, with a homogeneous liquid in the cell; the double stops are then lowered in front of the main aperture and a record of the two double slit patterns is made. From these, the mean distance between the centre of the reference trace and the optic axis of the apparatus is found. Provided the optic axis be horizontal, the two results agree very closely. The boundary is then formed between the two liquids and another photograph of the two double slit patterns is made, the double slit in front of the main aperture being arranged so that the boundary is between the two slits. This record is used to calculate the fractional part of j_m, the difference in optical path length between the two liquids in the cell, in wave-lengths of light; the integral part of j_m is found from the number of minima in the Gouy pattern. Finally, the double slit in front of the main aperture is raised and the flow of liquids through the cell channel is stopped. Photographs of the Gouy pattern and the reference trace are then taken at regular intervals after flow has stopped. A typical set of patterns, obtained in a measurement of this kind, is shown in Fig. 3. An abridged calculation of the diffusion coefficient of glycine from such a record is shown below.

The method finally adopted for introducing the two liquids into the cell while maintaining a sharp boundary between them was as follows. The liquids are contained in identical pipettes, the tips of which are bent through a right angle and drawn out to very fine jets. The pipettes are clamped above the cell with their tips on either side of the central partition, touching the cell walls immediately above the optically flat windows. The flow of liquids from the pipettes is controlled by rubber tubing, screw clips, and fine glass capillaries at their tops. The denser liquid is allowed to flow into the cell in the compartment farther from the channel, until it is above the channel level in both compartments, and liquid is then drawn through the channel. The denser liquid is delivered from the pipette at a very slow rate and the less dense liquid is allowed to flow into the cell compartment near the channel at a similar rate, both liquids being continuously drawn off through the channel. With care and practice, initial mixing of the liquids can be avoided. When the flow rates of the two liquids have been adjusted, the rate of withdrawal through the channel is reduced and columns of liquid are built up in the compartments of the cell. The inflow rates from the pipettes can be increased to about 0·5 ml./min. when the tips of the pipettes are covered. In later work, it was found necessary to build up large columns of liquids in the cell; provided great care be taken to avoid any initial mixing, about 10 ml. of each of them is sufficient. When sufficient quantities of the two liquids have been run into the cell, the pipettes are carefully removed and the slow rate of outflow through the channel is maintained for some time to ensure temperature equilibrium. The withdrawal rate is increased for a few minutes and then stopped completely at the start of the Gouy pattern measurements.

By these methods, the apparatus has been calibrated with " AnalaR " glycine as a standard substance. An abridged calculation is shown below.

Calculation of diffusion coefficient of glycine.—0·5000 G./100 ml. of solution diffusing into water.

Distance, centre-reference trace to optic axis	= 0·1651 cm.
Distance, centre-reference trace to centre of double slit pattern with boundary between slits	= 0·1853 cm.
Mean interband distance for double slit pattern	= 0·0252 cm.
Fractional part of $j_m = (0{\cdot}1853 - 0{\cdot}1651)/0{\cdot}0252$	= 0·80
Integral part of j_m	= 38

In the following table, t is the time (in seconds) after stoppage of flow at which the photograph is taken; j is the number of each interference pattern minimum, the outermost being numbered zero and the number increased as the undeviated slit image is approached; Y is the displacement of each minimum below the optic axis, in cm.; $f(z)$ is equal to $(j + 3/4)/j_m$ and e^{-z^3} is the displacement of each fringe derived from the theory of the process and interpolated from the tables given by Kegeles and Gosting (*loc. cit.*); C_t is the ratio of observed displacement to theoretical displacement and should be constant for a given pattern. The apparent diffusion coefficient D' is calculated from Longworth's equation $D' = b^2 j_m^2 \lambda^2 / 4\pi C_t^2 t$, where b is the optical distance from the centre of the cell to the photo plate (135·5 cm. in this case), λ is the wave-length of the light in cm., and $t = 180$ sec.

j	Y	$f(z)$	e^{-z^3}	C_t	j	Y	$f(z)$	e^{-z^3}	C_t
2	1·388	0·0709	0·798	1·739	14	0·721	0·380	0·411	1·755
4	1·239	0·122	0·711	1·743	16	0·638	0·432	0·364	1·753
6	1·113	0·174	0·638	1·744	18	0·559	0·483	0·320	1·748
8	1·002	0·226	0·573	1·748	20	0·483	0·535	0·278	1·737
10	0·904	0·277	0·514	1·759	22	0·420	0·586	0·239	1·757
12	0·809	0·329	0·461	1·755	24	0·353	0·638	0·209	1·748

Mean $C_t = 1{\cdot}749$; standard deviation = 0·007, standard error = 0·002.

At other values of t, mean values of C_t were :

t	180	360	720	1440
C	1·749	1·278	0·909	0·652
$10^5 D'$	1·192	1·116	1·103	1·072

The decrease of D' with increasing t was noted by Longsworth (*loc. cit.*), who attributed it to the fact that the boundary between the liquids is not infinitely sharp. He corrected for this by introducing a quantity Δt representing the time which an infinitely sharp boundary would take to reach the state of the boundary existing when flow is stopped; D' is then plotted against $1/t$ and the straight line is extrapolated to $1/t = 0$ to give the true value D of the diffusion coefficient. The slope of the line gives a measure of Δt.

In this case extrapolation gave $10^5D = 1{\cdot}05_9$ (cf. Lyons and Thomas, *J. Amer. Chem. Soc.*, 1950, **72**, 4506, who give 1·057) and $\Delta t = 24$ seconds.

The value of Δt is very much a function of the rate of flow of liquids through the channel just before it is stopped. With more rapid flow, the Δt effect can be reduced to the same order as the experimental error in C_t; *e.g.*, in a measurement with glycine (0·5 g. in 100 ml.) in which great care was taken to avoid initial mixing and a high rate of flow through the channel was maintained, the following results were obtained:

T	600	1200	2400	
C	0·903	0·638	0·450	
$10^5D'$	1·058	1·059	1·063	Mean = 1·060

showing that very sharp boundaries can be obtained by this flow technique.

The Gouy interference-pattern method is suitable for studying changes at the boundaries between optically clear liquids which do not interact to form cloudy products, though the theory for interpreting the patterns will have to be simplified by approximations in order to yield a physical picture of changes occurring as the boundary thickens, when more than two components are present. If turbidity appears at the boundary or if one of the liquids is not optically clear, the Gouy method is less useful, and in such cases the optical system of the apparatus has been modified so as to photograph directly the turbid areas in the cell. To do this, the lens C in Fig. 1 is set so as to give parallel light from the spectrometer slit which is opened to 100-μ aperture, and a new lens is put between the thermostat and the photographic plate to focus a direct image of the cell contents on to the plate. With this and the Gouy method, a wide variety of boundaries can be studied; the only limitations are that one liquid should be optically clear and that any materials formed at the interface should be sufficiently fluid to pass through the outflow channel of the cell.

Results.—In order to provide a background for more detailed physicochemical studies with materials of defined chemical constitution, the boundaries formed with some colloid sols of biological interest have been examined.

(1) *Interfaces between oppositely charged colloid sols.* The possibility of forming stable interfaces between sols carrying opposite electrical charges has been investigated, gelatin (positive) and acacia (negative) sols at pH 4 being used. These interact at room temperature to give a flocculent precipitate; at higher temperatures a completely liquid coacervate is formed (Kruyt, "Colloid Science," Vol. II, London, 1949, p. 255).

The sols were prepared so as to contain minimum concentrations of micro-ions. 2% Gelatin sols were made by dissolving low-ash gelatin in warm, recently boiled conductivity water; the sol was passed through a mixed-bed ion-exchange column (H form of Zeo-Karb 215 plus OH form of Amberlite IRA-400; cf. Kenchington and Ward, *Research*, 1951, **4**, 247) from which it emerged with a pH of 5·2 (this was independent of the relative proportions of the two resins) and a specific electrical conductivity reduced from 6×10^{-4} to 7×10^{-6} mho/cm., indicating almost complete removal of micro-ions. The gelatin was then precipitated with ethanol in the cold, filtered off, washed with cold water, redissolved in warm water, and dialysed against water to remove traces of ethanol; the sol was adjusted to pH 4 by addition of a few drops of N-hydrochloric acid. Acacia sols were prepared by dissolving the gum in conductivity water and shaking the solution with mixed ion-exchange resins to remove free micro-ions; the sol was then shaken with the H form of Zeo-Karb 215 alone until sufficient of the bound micro-cations (Ca, Mg, and K) were replaced by hydrogen ion to give a pH of 4.

Diffusion coefficients of the sols were measured by the Gouy method; the patterns agreed moderately well with theory and gave values of diffusion coefficients at 36° of $2{\cdot}4_3 \times 10^{-6}$ c.g.s. units for a 2% gelatin sol and $2{\cdot}7_5 \times 10^{-6}$ for a 1% acacia sol.

When boundaries were formed between the two sols in the cell at 36°, a very sharp interface was obtained during flowing, provided initial mixing of the sols was avoided; on mixing, they gave a dense white coacervate which was difficult to sweep out of the cell by running large volumes of liquid out through the channel. When flow was stopped, the boundary thickened steadily as the sols diffused into one another; the upper and the lower edge of the region of interaction remained quite sharp for up to an hour, and by direct photography the thickness of this turbid region could be estimated at different times. This thickness was found to be approximately a linear function of $\sqrt{t}$.

Boundary thickness, cm. ...	0·077 ± 0·006	0·100 ± 0·011	0·126 ± 0·012	0·180 ± 0·014
Time, t, sec.	300	600	1200	2400

The effects of some surface-active materials on the rate of thickening of this boundary were studied by injecting their solutions into the interface just after flow had stopped, by means of an Agla micro-syringe. No significant effects were observed.

(2) *Lecithin sols.* The film-forming properties of phospholipids are well known (*Adv. Protein Chem.*, 1949, **5**, 434) and it seemed possible that a material such as lecithin might form a stable film between aqueous liquids at the flowing interface.

A purified preparation of lecithin was made from commercial egg lecithin by cadmium chloride precipitation and light petroleum–ethanol partition (Pangborn, *J. Biol. Chem.*, 1945, **161**, 71). The resulting waxy solid was stored in an atmosphere of dry nitrogen, in the dark. It was not easily dispersed in water and 0·5% sols were prepared by dissolving the solid in a minimum amount of ether and adding this slowly to conductivity water with vigorous shaking; the ether was removed by evaporation at 40°/15 mm. The sol was invariably turbid and was little clarified by centrifugation. The difficulty of obtaining clear sols from egg lecithin has been described by McFarlane (*Discuss. Faraday Soc.*, 1949, **6**, 79). No further attempts were made to clarify these sols, and boundaries formed with them were examined by direct photography.

An extremely sharp, bright interface was formed by running the 0·5% sol against water (Fig. 4A); two hours after flow was stopped the interface was still bright and sharp and had moved very slightly (Fig. 4B), and a Gouy photograph through the clear upper liquid showed no lines due to diffusion from the interface, and even 20 hours later, the boundary was still sharp and bright (Fig. 4C) and had not moved appreciably. It was not until several days later that it began to appear diffuse, probably owing to decomposition of the lecithin. This remarkably stable sharp interface between two phases consisting mainly of water appears to be due to the formation of a fatty acid film at the boundary which may be bimolecular (a type of laminar micelle across the boundary) or it may consist of a number of bimolecular layers. A similar stable sharp boundary between deoxyribonucleic acid sols and water has been noted by Butler and James (*Nature*, 1951, **167**, 844); this boundary moved continuously, however, and they attributed its formation to the existence of a gel network in the sols; with lecithin, however, there is little likelihood of this since its sols are very mobile.

When the cell containing a lecithin sol–water interface was moved, the boundary showed little mechanical strength, and on injection of a solution of a cytolytic agent (tetradecylpyridinium bromide) just above the boundary, visible disruption occurred (Fig. 4D).

(3) *Serum albumen and lecithin sols.* If lecithin can cause a relatively stable fatty acid film to spread at the flowing interface, it seems reasonable to suppose that a protein which is denatured at an oil–water interface might form a mixed surface layer with the lecithin and provide a backbone for the fatty acid film, giving it some mechanical strength. To test this idea, a boundary was formed between 0·5% lecithin and bovine serum albumen sols (made from recrystallised material supplied by Armour laboratories). A sharp boundary was obtained at first, but after 1 hour penetration of the clear albumen sol by the lecithin was evident. A mixed sol of lecithin and albumen was then caused to flow against water; a sharp turbid sol–clear liquid boundary was obtained, but after 2 hours a Gouy photograph taken through the clear liquid showed lines due to diffusion, and after 20 hours a second sharp boundary appeared above the original one.

On injection of an albumen sol above a lecithin sol–water interface, the protein appeared to spread over the boundary. After 20 hours, the boundary remained sharp, and when the cell was moved it showed some mechanical strength, settling back to its original position even after considerable movement of the cell. This suggests that a protein film is formed at the boundary, and this technique may provide the answer to the problem stated by Langmuir and Waugh.

Discussion

It appears that lecithin sols have the property of forming stable interfacial films between aqueous liquids, and there is evidence that these films can be strengthened by injection of a serum albumen sol at the interface. Mixed films of this type should provide a useful model for the study of biological adsorption of organic compounds, since they can be formed in apparatus in which their optical and electrical properties can be readily studied.

Lecithin is not a well-defined chemical entity, and it would be desirable to produce fatty acid films between aqueous liquids from materials of better known composition. The formation of these stable boundary layers is likely to be related to the production of myelin forms by lecithin in contact with water, and since the latter property is also shown by other fatty materials (Dervichian and Magnant, *Bull. Soc. Chim. biol.*, 1946, **28**, 419), it is likely

that other fatty sols or solutions will be capable of forming stable interfaces between aqueous liquids. Further work will be directed towards the study of diffusion and membrane formation at the flowing interface, with aqueous solutions of surface-active materials of known constitution.

The author thanks Professor W. H. Linnell for his interest and support and for helpful discussions which led to the initiation of this work; he also thanks the Central Research Fund of the University of London for a grant towards the cost of equipment, and Mr. P. C. Barden for his accurate work in constructing the diffusion apparatus.

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106. *The Chemistry of Mould Metabolites. Part I. Isolation and Characterisation of a Red Pigment from* Coriolus sanguineus *(Fr.).*

By G. W. K. CAVILL, B. J. RALPH, J. R. TETAZ, and R. L. WERNER.

Naturally occurring and the artificially grown *Coriolus sanguineus* contain a compound, $C_{14}H_{10}O_5N_2$, believed identical with Lemberg's polystictin and Gripenberg's cinnabarin, which is shown by chemical and spectroscopic studies to contain an acidic hydroxyl group, an amide group, and possibly an ether link. The basic skeleton is of a polycyclic unsaturated type containing a quinonoid system and heterocyclic nitrogen.

A BRIGHT-RED wood-rotting fungus, *Coriolus sanguineus* (Fr.), is a conspicuous feature on decaying pines and eucalypts in the natural bushlands close to Sydney. This fungus would seem to be cosmopolitan in distribution and, as there is considerable variation in its general appearance and colour, it is not surprising that it is known by many synonyms: *Polyporus cinnabarinus* Fr., *P. sanguineus*, Fr., *P. coccineus*, Fr., *P. puniceus*, Kalch; *Polystictus cinnabarinus* (Jacq.), *P. sanguineus*, L., *P. semi-sanguineus*, Lloyd, *Trametes cinnabarina* (Jacq.), Fr. In the herbarium of the Royal Botanical Gardens, Kew, Australian specimens are placed under the names *Polystictus sanguineus* and *P. cinnabarinus*, but it is the opinion of Cunningham (*Proc. Linn. Soc. N.S.W.*, 1950, **75**, 240), who has recently re-examined the type specimens, that the collections should be merged under the name of *Coriolus sanguineus* (Fr.).

Recently, as the result of one afternoon's collecting in the vicinity of Sydney, over 5 kg. of fresh fungus were obtained. The same red pigment is isolated from cultures grown on synthetic medium (described below) as from the natural fungus. Lemberg [Report of Nat. Health and Med. Res. Council, C'wealth of Australia (Canberra), 1946, p. 12; *Aust. J. Exp. Biol. Med. Sci.*, 1952, in the press] reported the isolation of a red nitrogenous pigment, polystictin, from the Australian fungus, *Polystictus cinnabarinus*, and, in Finland, Gripenberg (*Acta Chem. Scand.*, 1951, **5**, 590) has described the isolation of the red pigment cinnabarin from *T. cinnabarina*. We therefore record our studies on the chemistry of the red mould metabolite from *C. sanguineus* (Fr.). It appears that these compounds are the same, and we retain the name polystictin.

Polystictin is a red crystalline compound, $C_{14}H_{10}O_5N_2$, which decomposes above 320°. No satisfactory determination of the molecular weight of polystictin or its simple derivatives has yet proved possible, but on present chemical evidence, and in agreement with Gripenberg (*loc. cit.*), we believe the above formula a likely one. The pigment is extremely insoluble in most organic solvents, readily soluble in cold concentrated sulphuric acid to a deep violet solution, whilst in cold 2N-sodium hydroxide the colour is violet, changing to a dull red. Polystictin is slowly soluble in cold 3N-sodium carbonate and in saturated sodium hydrogen carbonate solution on slight warming. It can be regenerated from alkaline solution.

With diazomethane, or with methyl iodide or methyl sulphate and potassium carbonate in acetone, polystictin gives a monomethyl ether (a red acidic crystalline compound, possibly $C_{15}H_{11}O_6N$, is obtained as a by-product with methyl sulphate and potassium carbonate) which, in contrast to polystictin, is very readily soluble in dilute mineral acid and insoluble in cold 2N-sodium hydroxide. With acetic anhydride–sulphuric acid it gave an acetate,

insoluble in dilute mineral acid but slowly soluble in cold 3N-sodium carbonate. Thus, polystictin contains a hydroxyl group, to which we attribute its acidity. *O*-Methylpolystictin gives no colour with triphenyl borate in dioxan, whereas polystictin shows an orange-red solution after several minutes, suggesting that the free hydroxyl group is *peri* to a carbonyl system (Anderson, O'Brien, and Reuter, *Anal. Chem. Acta*, 1952, in the press).

A pale yellow "diacetylanhydrotetrahydrocinnabarin, $C_{18}H_{16}O_6N_2$," m. p. 200—202°, was obtained by Gripenberg on reductive acetylation of cinnabarin. We isolated an apparently identical compound, m. p. 200—204°, by this method but an acetyl estimation shows the presence of three such groups, and we believe this compound is triacetylanhydrodihydropolystictin, $C_{20}H_{16}O_7N_2$. Reductive acetylation of *O*-methylpolystictin gave a pale yellow, neutral, triacetyldihydro-*O*-methylpolystictin, without loss of water. We assume that a quinonoid system was reductively acetylated, and that the molecule of water lost from polystictin involved the hydroxyl group which was methylated. We have still to account for an additional acetyl group present in the reduction products.

Polystictin is reductively benzoylated by benzoyl chloride and sodium dithionite in cold sodium hydroxide solution, to a tetrabenzoyldihydropolystictin insoluble in cold mineral acid and alkali. The quinonoid structure is also supported by the ease with which polystictin is reduced with zinc and dilute acid and re-oxidised on exposure to the atmosphere. There is no apparent reaction between polystictin and *o*-phenylenediamine.

Ammonia and carbon dioxide are evolved on hydrolysis of polystictin with warm aqueous barium hydroxide, followed by acidification. These products are presumably derived from an amide (or imide) group, which is converted into a carboxylic acid, capable of ready decarboxylation.

The following infra-red spectroscopic evidence confirms and supplements the chemical examination. The spectrum of solid polystictin in the high-frequency region (Fig. A), which is the same irrespective of the source of the compound, consists of three sharp bands. That at 3505 cm.$^{-1}$ is normally associated with the hydroxyl group; the other two, of the longer wave-length, are assigned to the two hydrogen atoms attached to a nitrogen of a primary amine or of an unsubstituted amide (Williams, Hofstadter, and Herman, *J. Chem. Phys.*, 1939, **7**, 802). Around 2900 cm.$^{-1}$, where one normally expects to find the –C–H bands associated with saturated carbon, polystictin is transparent, indicating an almost, if not complete, lack of such groups. However, the presence of unsaturated =C–H groups is shown by the band at 3165 cm.$^{-1}$, suggesting an unsaturated polycyclic system.

There are two bands, at 1672 and 1653 cm.$^{-1}$, of which the former is the more intense, and such bands (of similar intensity) have been assigned to the >C=O and $-NH_2$ groups, respectively, of an amide (Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," New York, 1949, p. 10). A simple carbonyl group conjugated to an aromatic nucleus, as in acetophenone, would explain the 1672-cm.$^{-1}$ band but there is no chemical evidence for such, nor are there spectroscopic features in the 3- and 4-μ regions characteristic of a carboxylic acid. It is more difficult to rule out the possibility of an unconjugated –C=N– system; were it conjugated with –C=C– groupings, as is probable, it would move to longer wave-lengths and become indistinguishable as part of the ring vibrations between 1600 and 1480 cm.$^{-1}$ (Angyal and Werner, *J.*, 1952, 2911; Blout, Fields, and Karplus, *J. Amer. Chem. Soc.*, 1948, **70**, 194). Both the 3- and the 6-μ bands therefore support the suggestion that an amide group is present.

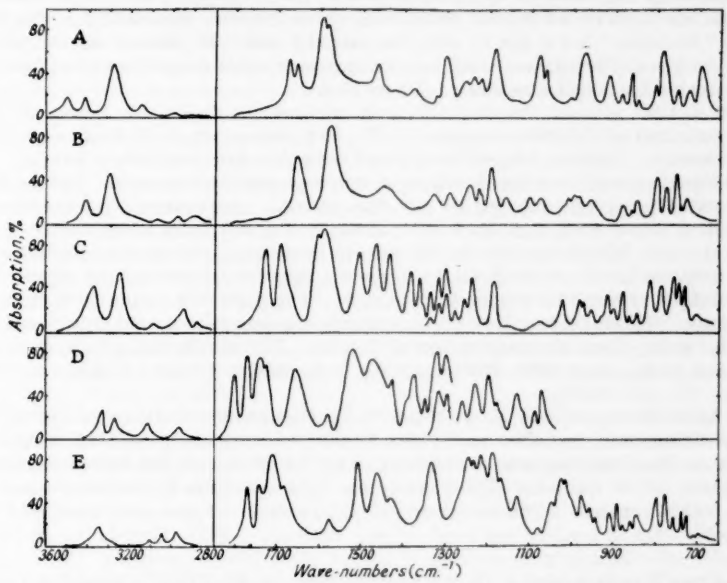
Polystictin gives intense bands at 1600 and 1586 cm.$^{-1}$, which are normally associated with the ring vibrations of unsaturated cyclic systems, including quinonoid structures. Further, the absence of bands at 1380 and 1450 cm.$^{-1}$ confirms the lack of $-CH_2$ and $-CH_3$ groups while the 1466-cm.$^{-1}$ band is suggestive of the bending vibration of hydrogen attached to unsaturated carbon (Thompson and Torkington, *Trans. Faraday Soc.*, 1945, **61**, 250).

The spectrum of *O*-methylpolystictin (Fig. B) shows the expected conversion of a hydroxyl into a methoxyl group and that of *O*-acetylpolystictin (Fig. C) indicates the conversion into an acetoxy-group (cf. Barnes, Gore, Liddel, and Williams, "Infra-Red Spectroscopy," New York, 1944, pp. 67, 68). In all three compounds there are strong

bands in the 700—800-cm.$^{-1}$ region, usually associated with nuclear substitution, but it remains for the basic system to be identified before information can be obtained from these bands.

The most striking feature of the spectra of the two compounds produced by reductive acetylation (Figs. D and E) is the change in the ring vibrations. The strong bands around 1600 cm.$^{-1}$ have been replaced by bands of lower frequency, between 1400 and 1600 cm.$^{-1}$, which indicate a new common structure. The new system is unusual in that strong bands are now present around 1500 cm.$^{-1}$ rather than higher, and it may be significant that a shift to longer wave-lengths has been observed in heterocyclic nitrogenous compounds or where several rings are fused together (Canon and Sutherland, *Spectrochim. Acta*, 1951, **4**, 373). Reductive acetylation also introduced a number of bands above 1700 cm.$^{-1}$, three of which appear to be due to common structures, namely, at 1722, 1736, and 1769

Infra-red spectra of polystictin and some derivatives.



A, *Polystictin*. B, O-*Methylpolystictin*. C, O-*Acetylpolystictin*. D, *Reduced acetylated polystictin*. E, *Reduced acetylated O-methylpolystictin*.

cm.$^{-1}$ in the reduced polystictin and at 1709, 1730, and 1768 cm.$^{-1}$ in the reduced *O*-methylpolystictin, and these are assigned to acetate groups. There is a further band at 1799 cm.$^{-1}$ in the reduced polystictin indicative of the carbonyl group in a β-lactam or other strained ring system. In all the spectra a sharp band of medium intensity near 1190 cm.$^{-1}$ may be assigned to an ether linkage, unaffected by any of the reactions described.

It is concluded that polystictin contains an amide group, and an acidic hydroxyl group most likely *peri* to a carbonyl group, itself being part of a quinonoid structure. In the absence of a positive test for a nitrogenous system we believe the second nitrogen atom to be heterocyclic and that this is acetylated during the reductive acetylation. The fifth oxygen atom is accommodated as an inert ether link. Finally, in the absence of methylene and methyl groups, we assume the remaining carbon and hydrogen to be part of the fundamental unsaturated polycyclic system. Degradative studies on polystictin and its derivatives are in progress and will be reported later.

Experimental

The Fungus.—The sporophores varied in colour from a bright vermilion to a very dark blood-red. The fruiting bodies are commonly laterally attached throughout, but many speci-

mens are thin and coriaceous and attached by a short stem, such characteristics being generally considered to be typical of the tropical forms, usually described as *Polystictus sanguineus* L. Our experience indicates much variation in the characteristics of the pure cultures derived from different forms of the organism, and some current investigations are directed towards the detection of corresponding variations in metabolism.

Isolation of Polystictin.—(a) *From naturally occurring* Coriolus sanguineus. The following is typical of numerous isolations. The dried, milled fungus (8 × 50 g.) was extracted (Soxhlet) with acetone. To the vermilion solid (3·45 g.) which separated from the extracts was added the waxy material (2·5 g.) obtained on evaporation of the combined filtrates. The total solid (5·95 g.) was washed with hot alcohol (2 × 200 ml.), giving crude polystictin (3·5 g.). Repeated treatment of this (1·0 g.) with boiling dioxan gave *polystictin* (0·3 g.) as red needles, decomp. >300° (Found : C, 58·9; 58·3, 58·3; H, 3·9, 3·6, 3·4; N, 9·0, 9·4, 9·9. $C_{14}H_{10}O_5N_2$ requires C, 58·7; H, 3·4; N, 9·8%), difficultly soluble in organic solvents (acetone, 0·04% at 20°; dioxan, 0·1% at 100°), fairly soluble in cold concentrated hydrochloric acid.

(b) *From fungi cultivated on artificial medium.* The following pure fungal cultures were grown as surface mats on a modified William–Saunders medium (*Biochem. J.*, 1934, **28**, 1887) containing " Marmite " (0·1 g. per l.) with glucose (50 g. per l.) in place of sucrose, and glycine (2 g. per l.) in place of asparagine. All inoculations were made with slips of mycelium-covered agar from stock slope cultures on Sabaraud's medium.

(i) Culture 105A (Forest Products Research Laboratories Collection, Princes Risborough, England), described as *Polystictin sanguineus* (L.) Mey, was grown in 66 flasks each containing 500-ml. of medium. Approx. 10 g. of cotton wool were placed in each flask to form an " island " to support initial growth since the mycelium of this organism tends to sink. The organism was grown for 257 days at 25°, followed by 543 days at room temperature; the mycelium was a light vermilion colour with some dark-red patches and a few fluffy white areas; there were numerous abortive fructifications. At the time of harvesting, the mycelium could be readily separated from the cottom wool which was stained a light brown, and did not appear too much degraded since it retained its mechanical strength. The yield of vacuum-dried mycelium was 4·5 g. per flask. This mycelium (175 g.), on extraction, gave a brown solid (1·6 g.) and a further tarry residue (0·9 g.) from the evaporation of filtrates. Polystictin (0·16 g.) was finally isolated as orange-red prisms, m. p. 300—320° (decomp.), from dioxan (600 ml.) (Found : C, 58·8, 58·9; H, 3·9, 3·8; N, 10·2, 10·0%).

[With Anne Edwards and J. G. Wilson] (ii) Culture 6D (Division of Forest Products Collection, Melbourne), described as *T. cinnabarina*, and originally isolated in 1947 from a sporophore on *Eucalyptus regnans*, was grown at 30° for 49 days in 102 flat-sided bottles, each containing 150 ml. of medium. The yield of the light vermilion mycelium, washed and air-dried, was 0·54 g. per flask. This mycelium (55 g.) on extraction gave a red waxy solid (1·65 g.), yielding polystictin (0·1 g.) as light red prisms, decomp. >300° (Found : C, 58·0; H, 3·8; N, 9·5%).

[With Anne Edwards and J. G. Wilson] (iii) Culture 6F (D.F.P.), from the Department of Agriculture, Ottawa (Culture Collection No. 17765), described as *Polyporus cinnabarinus*, was originally isolated in 1946 from a sporophore on *Acer rubrum*. It was grown as in (ii) (103 bottles) for 41 days, the yield being 0·58 g. per flask. This mycelium (60 g.) was treated as above, yielding polystictin (0·01 g.) which crystallised in light red-brown prisms (from dioxan), decomp. >300° (Found : C, 57·8; H, 3·5%).

Acetylation of Polystictin.—Polystictin (0·5 g.) was added to sulphuric acid (36N; 1 ml.) and acetic anhydride (10 ml.) and after 10 min. the black solution was poured on ice. The resulting red solid was extracted with chloroform and the extract treated with sodium hydrogen carbonate solution, removing a red fluorescent compound. O-*Acetylpolystictin* (0·13 g.), isolated on evaporation of the washed and dried chloroform solution, crystallised as red needles, m. p. 250—252° (decomp.), from acetone–light petroleum (Found : C, 58·1; H, 3·5; N, 8·4. $C_{16}H_{12}O_6N_2$ requires C, 58·5; H, 3·7; N, 8·5%). Acetylation in aqueous alkali or pyridine failed.

O-*Methylpolystictin.*—(*a*) Polystictin (1·5 g.) was suspended in dry acetone (1500 ml.) with potassium carbonate (30 g.) and methyl sulphate (9 ml.) and refluxed for 7 hours. The crude product, after filtration and evaporation of acetone, was taken up in chloroform. Extraction of the chloroform solution, with sodium hydrogen carbonate solution, followed by acidification, gave a *substance* (0·02 g.) as red prisms, m. p. >200° (decomp.), from ethyl acetate–light petroleum (Found : C, 57·7, 59·2; H, 3·5, 3·7; N, 4·7, 4·3. $C_{15}H_{11}O_6N$ requires C, 59·8; H, 3·7; N, 4·6%). O-*Methylpolystictin* (0·4 g.) was obtained on evaporation of the

washed and dried chloroform extract and crystallised as orange-red prisms, m. p. 200—202° (decomp.), from ethyl acetate–light petroleum (Found: C, 60·2; H, 3·8; N, 9·1; OMe, 8·3. $C_{14}H_9O_4N_2$·OMe requires C, 60·0; H, 4·0; N, 9·3; OMe, 10·3%).

(*b*) Methylation as above, with methyl iodide instead of methyl sulphate, gave *O*-methylpolystictin (0·3 g.), orange-red prisms, m. p. 222—223° (decomp.), from acetone–light petroleum or from ethyl acetate–light petroleum (Found: C, 60·2; N, 4·0; N, 9·5%).

(*c*) Methylation of polystictin (2 g.) with ethereal diazomethane in methanol (30 ml.) and water (10 ml.) gave unchanged polystictin (1 g.) and *O*-methylpolystictin (0·04 g.), which crystallised as orange-red prisms, m. p. 236—240° (decomp.), from ethyl acetate (Found: C, 60·3; H, 4·2; H, 9·3%). It is extremely difficult to obtain reproducible m. p.s for *O*-methylpolystictin, the decomposition temperature depending on the rate of heating.

Reductive Acetylation of Polystictin.—Polystictin (0·7 g.) with zinc dust and acetic anhydride (20 ml.) in the presence of pyridine yielded a *substance* (isolated by Gripenberg's method) as yellow plates, m. p. 200—204°, from ethyl acetate–acetone (Found: C, 59·7; H, 3·7; N, 7·5%). Sublimation at 200—220°/7 × 10^{-3} mm. gave a yellow solid, m. p. 195°, mixed m. p. with compound above 196° (Found: C, 60·5, 60·1; H, 4·0, 4·0; N, 7·3, 7·4; 3Ac, 33·7. $C_{20}H_{16}O_7N_2$ requires C, 60·6; H, 4·0; N, 7·1; 3Ac, 32·6%).

Reductive Acetylation of O-*Methylpolystictin.*—Treatment of *O*-methylpolystictin (0·6 g.) as described for polystictin gave a yellow *substance* (0·4 g.), crystallising in yellow needles, m. p. 156°, from acetone–light petroleum (Found: C, 59·0, 58·2; H, 5·2, 4·6; N, 6·2, 6·3; OMe, 6·5; 3Ac, 34·4. $C_{21}H_{20}O_8N_2$ requires C, 58·8; H, 4·7; N, 6·5; OMe, 7·2; 3Ac, 31·5%).

Regeneration of Polystictin from Alkaline Solution.—Polystictin (0·14 g.) was dissolved in cold dilute sodium hydroxide solution, and the purple-red filtered solution acidified at 10—20° with concentrated hydrochloric acid. The red solid which separated recrystallised from dioxan (300 ml.) as red needles (0·02 g.) (Found: C, 58·1; H, 3·6; N, 9·4%).

Reductive Benzoylation of Polystictin.—Addition of benzoyl chloride (10 ml.) to polystictin (1 g.) dissolved in dilute sodium hydroxide solution containing excess of sodium dithionite gave a yellow solid on shaking. The crude product was extracted with chloroform, and the solution washed with sodium hydrogen carbonate solution. Evaporation of the chloroform layer gave the *substance* (0·15 g.) as an oil, which on repeated crystallisation, gave an ill-defined solid, m. p. 98 104°, from ethanol [Found: C, 72·4, 71·3; H, 4·1, 3·9; N, 3·3, 4·0. $C_{14}H_8O_5N_2(C_6H_5{\cdot}CO)_4$ requires C, 71·6; H, 4·0; N, 4·0%].

Alkaline Degradation of Polystictin.—Polystictin (1·5 g.) was refluxed with 2N-barium hydroxide (100 ml.) for 1 hour, and the alkaline distillate was collected in N-hydrochloric acid. After evaporation of the distillate and addition of chloroplatinic acid, yellow prisms of ammonium chloroplatinate separated [Found: N, 6·3. Calc. for $(NH_4)_2PtCl_6$: N, 6·3%]. Acidification of the residual barium hydroxide solution and distillation liberated carbon dioxide, identified as barium carbonate.

Identifications.—Analyses of polystictin and its derivatives vary considerably within replicates and much difficulty is also experienced with m. p.s of other than the reduced acetylated compounds. However, infra-red spectroscopic examination of all samples of polystictin, *O*-methylpolystictin, and other derivatives from their respective sources confirmed the identities in each case.

Infra-red Spectra.—Infra-red spectra of the different samples of polystictin and its derivatives were recorded with a Perkin-Elmer Model 12-C spectrometer with sodium chloride optics. This instrument was calibrated against ammonia, water vapour, and carbon dioxide from the data of Oetjen, Kao, and Randall (*Rev. Sci. Instr.*, 1942, **13**, 515) and comparison with the data used indicated a resolving power of about 2 cm.$^{-1}$ at 1000 cm.$^{-1}$, 5 cm.$^{-1}$ at 1700 cm.$^{-1}$, and 20 cm.$^{-1}$ at 3000 cm.$^{-1}$. Each sample was run as a paste with paraffin oil according to the method of Randall *et al.* (*op. cit.*), and also as a mull with tetrachloroethylene which has been found suitable to cover the C–H regions obscured by the paraffin oil. The percentage transmission recorded may not correctly indicate the percentage absorption to any better than 5% because of differential scattering from the solid particles.

We thank Dr. E. Challen and Miss B. Stevenson of this School for C, H, and N microanalyses, and the staff of the Organic Microanalytical Laboratory, C.S.I.R.O., Melbourne, for methoxyl and acetyl determinations.

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Sydney, Australia. [*Received, September 10th*, 1952.]

107. *The Reaction of Diborane with the Alkyl Derivatives of Some Group* VB *Elements.*

By F. Hewitt and A. K. Holliday.

With Group VB trialkyls M, diborane yields borine co-ordination compounds $\overset{+}{M}-\overset{-}{B}H_3$. The effect of change of donor atom and of alkyl group on the thermal stability of these compounds is discussed, and their reaction with hydrogen chloride is investigated.

Although borine normally exists only as the dimer diborane, the latter can undergo fission in the presence of a donor molecule M to give compounds $\overset{+}{M}-\overset{-}{B}H_3$ in which the borine group is stabilised by co-ordination. Known compounds of this type include those with M = Me_3N, CO, and Me_2O (Schlesinger and Burg, *J. Amer. Chem. Soc.*, 1937, **59**, 780; 1938, **60**, 290). The trialkyls of the Group VB elements generally act as donor molecules to form 1 : 1 co-ordination compounds with electron-acceptor molecules BX_3 (other than borine), *e.g.*, $Me_3\overset{+}{P}-\overset{-}{B}Me_3$ (Brown and Harris, *ibid.*, 1949, **71**, 2751), $Me_3\overset{+}{P}-\overset{-}{B}Br_3$ (Holliday and Mowle, unpublished work), $Et_3\overset{+}{N}-\overset{-}{B}F_3$ (Kraus and Brown, *J. Amer. Chem. Soc.*, 1929, **51**, 2690): similar compounds with the Group III analogues of BX_3 have been obtained. The relative stabilities of the 1 : 1-compounds of trimethylgallium with the trimethyl derivatives of all the Group VB elements have been discussed by Coates (*J.*, 1951, 2003). We have, therefore, investigated the reactions of diborane with several Group VB trialkyls, with the object of obtaining co-ordination compounds of borine and, if possible, of studying the effect on stability and other properties of (*a*) change of donor atom and (*b*) change of alkyl groups in the donor molecule.

Table 1.

Compound	M. p.*	V. p. (25°), mm.	Temp. of decompn.	Products of decompn., 120°	Moles of H_2 per 100 moles of compound
$Me_3\overset{+}{N}-\overset{-}{B}H_3$ †	94°	0·9	>125°	Unchanged	0
$Me_3\overset{+}{P}-\overset{-}{B}H_3$ ‡	100 *	40	80—90	H_2, CH_4	2·6
$Me_3\overset{+}{As}-\overset{-}{B}H_3$	72 *	~3	40—50	H_2, CH_4	5·4
$(Me_3\overset{+}{Sb}-\overset{-}{B}H_3)$	−35 *	—	−35	H_2	~26
$Et_3\overset{+}{P}-\overset{-}{B}H_3$	46	62	60—70	H_2	7·4
$Et_3\overset{+}{As}-\overset{-}{B}H_3$	40 *	~1	30—40	H_2	14·8
$(n\text{-}Pr_3\overset{+}{P}-\overset{-}{B}H_3)$	~11	10	40—50	H_2	~20

* Indicates decomposition. † Data from Schlesinger and Burg, *loc. cit.*

‡ Also prepared recently (1951) by Burg *et al.* (unpublished), who find hydrogen and methane in the thermal decomposition products.

When excess of diborane was condensed on the solid trialkyl at liquid-nitrogen temperature, and the temperature allowed to rise, reaction commenced and crystals appeared at the liquid–liquid interface. When reaction had ceased, unchanged reactants were removed, and the remaining solid purified by sublimation. Analysis and molecular-weight determination showed that for each trialkyl used, a 1 : 1-compound $\overset{+}{M}-\overset{-}{B}H_3$ was formed. When tri-*n*-propylphosphine was used, separation of the 1 : 1-compound was incomplete, and an impure product resulted. With trimethylstibine, crystals were formed which melted at −35°, but completely dissociated above this temperature. The compounds obtained, together with some of their properties, are listed in Table 1. With the two exceptions noted, all the compounds formed well-defined crystals, with an appreciable vapour pressure at room temperature, soluble in most organic solvents, insoluble in, but slowly hydrolysed by, cold water, and readily attacked by aqueous oxidants, *e.g.*, hydrogen peroxide and nitric acid. When they are heated *in vacuo*, irreversible decomposition occurs, often

below the m. p. To determine the temperature range over which decomposition begins, vapour-pressure measurements were made for 10° increments, the temperature being increased and decreased over each 10° range before the next increment was made. The lowest range over which the ascending and descending v. p.–T curves were non-concurrent gave the decomposition range (see Table 1). Thermal decomposition was further studied by heating the compounds in a sealed tube for 3 hours at 120°. From those containing methyl groups, hydrogen and a little methane were identified as volatile products; the other compounds yielded no hydrocarbon. Small amounts of other volatile products were obtained but not identified; some evolved hydrogen on storage, and it is probable that they were higher hydrides of boron.

A quantitative criterion of stability—the dissociation constant for the reaction $\overset{+}{M}\text{–}\overset{-}{B}H_3 \longrightarrow M + BH_3$—cannot be obtained from the above data because of irreversible secondary decomposition; but it is reasonable to suppose that this dissociation must be the important initial step in decomposition: and as the donor part of the molecule is thermally stable, the decomposition products must be chiefly those formed by interaction of the borine radicals. In Table 1, therefore, the hydrogen produced per mole of each compound is given, as a measure of the extent of thermal decomposition at 120°. This, together with the temperature of initial decomposition, gives two qualitative stability criteria which may be used to compare the compounds listed.

Effect of Change of Donor Atom on Stability.—For the trimethyl compounds, both criteria indicate an order of stability N>P>As>Sb, *i.e.*, decreasing with increasing size of donor atom; the same order was observed for compounds of Group V trialkyls with trimethylgallium (Coates, *loc. cit.*), trimethylaluminium (Brown and Davidson, *J. Amer. Chem. Soc.*, 1942, **64**, 316) (N>P), and trimethylboron (Brown, unpublished; see Chatt, *J.*, 1951, 652) (N>P>As) as acceptors.

Effect of Change of Alkyl Groups on Stability.—For the phosphorus compounds, both criteria indicate a stability sequence Me>Et>Pr^n, and for arsenic Me>Et (the low stability of PPr^n_3–BH_3 and its appreciable dissociation at ordinary temperature is responsible for the difficulty of isolating this compound). These results may be compared with those of Brown, Taylor, and Sei Sujishi (*J. Amer. Chem. Soc.*, 1948, **70**, 2878; 1951, **73**, 2464) for trimethyl boron with alkylamines as donors, *i.e.*, $R_3\overset{+}{N}\text{–}\overset{-}{B}Me_3$, where a stability order Me>Et<Pr^n<Bu^n< . . . was found. These authors suggest that conflicting steric requirements of the amine alkyl and the boron-attached methyl groups become important with the triethylamine compound, leading to a fall in stability; with larger alkyl groups the effect is modified by the increased inductive effect of the alkyls, and stability increases again, although rather slowly. In the present case, the greater size of the donor atom (P or As) and the presence of boron-attached hydrogen rather than methyl may make steric factors less important for methyl and ethyl than for *n*-propyl and higher alkyls. At the same time, the smaller inductive effect which the alkyls can exert, owing to the larger donor atom, may make the steric factors generally of predominant importance, bringing about the observed regular fall in stability with increasing size of alkyl.

The formation of a trace of methane in the decomposition of the trimethyl compounds may arise from the reaction $x\text{Me}_3\overset{+}{\text{P}}\text{–}\overset{-}{\text{B}}\text{H}_3 \longrightarrow (\text{Me}_2\text{P,BH}_2)_x + x\text{MeH}$ occurring simultaneously with dissociation [cf. the decomposition $R_3'\overset{+}{N}\text{–}\overset{-}{B}R_3 \longrightarrow R_2'N{:}BR_2 + R'R$ (Wiberg, F.I.A.T. Review 1949, Inorganic Chemistry, Part I, p. 129)]. In support of this mechanism, $Me_2H\overset{+}{P}\text{–}\overset{-}{B}H_3$, when heated to 150° yields hydrogen and the trimer and tetramer of $Me_2\dot{P},\dot{B}H_2$—both of these are chemically inert and thermally stable (Burg *et al.*, unpublished). The triethyl compounds $Et_3\overset{+}{P}\text{–}\overset{-}{B}H_3$ and $Et_3\overset{+}{As}\text{–}\overset{-}{B}H_3$ do not yield ethane on decomposition, possibly because the dissociation into borine and donor molecule is more readily achieved than the removal of an ethyl group from the donor atom.

The phosphorus and arsenic compounds listed in Table 1 all reacted vigorously with excess of hydrogen chloride on being warmed from liquid-nitrogen temperature. Hydrogen was evolved and, for the four compounds given in Table 2, the amount was measured

TABLE 2.

Compound	C.c. at N.T.P. Amount used	H_2 evolved $= x$	Amt. reacted $= x/3$	HCl used $= y$	$3y/x$
$Me_3\overset{+}{P}-\overset{-}{B}H_3$	7·10	12·8	4·27	16·0	3·75
$Me_3\overset{+}{As}-\overset{-}{B}H_3$	5·41	13·1	4·37	18·6	4·25
$Et_3\overset{+}{P}-\overset{-}{B}H_3$	3·80	7·77	2·59	11·4	4·38
$Et_3\overset{+}{As}-\overset{-}{B}H_3$	2·80	8·10	2·70	16·2	6·00

afte rone week at room temperature, together with the amount of hydrogen chloride used The results show that the amount of hydrogen was less, and the amount of hydrogen chloride greater, than that required by the equation $Et_3\overset{+}{P}-\overset{-}{B}H_3 + 3HCl \longrightarrow Et_3\overset{+}{P}-\overset{-}{B}Cl_3 + 3H_2$. No other gas or volatile product was formed. If the above equation is assumed to represent the main reaction, and if it is also assumed that the extent of this reaction is given by the amount of hydrogen evolved, then the last column of Table 2 shows that the molar excess of hydrogen chloride is approximately equal to the number of mols. of $\overset{+}{M}-\overset{-}{B}Cl_3$ compound formed, for the first three of the listed compounds. It is difficult to account for this fact other than by assuming the formation of a hydrochloride, *i.e.*, $\overset{+}{M}-\overset{-}{B}Cl_3 + HCl \longrightarrow [MH]^+[BCl_4]^-$. There is some indirect evidence for the formation of the $[BCl_4]^-$ ion in the compounds $NOCl,BCl_3$ and PCl_5,BCl_3 which may exist in the solid state as $[NO]^+[BCl_4]^-$ and $[PCl_4]^+[BCl_4]^-$ respectively (cf. Martin, *J. Phys. Chem.*, 1947, **51**, 1400). In addition, Wiberg and Heubaum (*Z. anorg. Chem.*, 1935, **222**, 98) have prepared the stable, crystalline, involatile compound CPh_3Cl,BCl_3 which may be formulated as $[CPh_3]^+[BCl_4]^-$. Simple alkali chloroborates, *e.g.* $NaBCl_4$, have never been prepared, in contrast to the well-known fluoroborates; the presence of a large cation may therefore be an essential prerequisite to the formation of a chloroborate.

The initial product $\overset{+}{M}-\overset{-}{B}Cl_3$ believed to be formed in the reaction with hydrogen chloride is readily prepared by direct addition of the trialkyl donor molecule to boron trichloride (*e.g.*, $Me_3\overset{+}{P}-\overset{-}{B}Cl_3$; Phillips, Hunter, and Sutton, *J.*, 1945, 146). If the reaction product, containing the presumed hydrochloride and unchanged $\overset{+}{M}-\overset{-}{B}H_3$, was gently heated *in vacuo*, the latter sublimed off, and the residue was found to have approximately the same m. p. as the corresponding $\overset{+}{M}-\overset{-}{B}Cl_3$ compound formed by direct addition (*e.g.*, with triethylphosphine as donor, the product had m. p. 62°; $Et_3\overset{+}{P}-\overset{-}{B}Cl_3$ prepared by direct addition had m. p. 65°). Hence, if a hydrochloride was formed, loss of hydrogen chloride occurred on heating it; the amount lost was not, however, determined. No reaction was observed when hydrogen chloride was condensed on $Me_3\overset{+}{As}-\overset{-}{B}Cl_3$, all the hydrogen chloride being recovered on warming the mixture to room temperature. Evidence for hydrochloride formation is therefore inconclusive, and further study is required.

The reverse reaction, *i.e.*, reduction of compounds $\overset{+}{M}-\overset{-}{B}Cl_3$ to $\overset{+}{M}-\overset{-}{B}H_3$, was attempted by using lithium aluminium hydride in ethereal solution. No reaction was observed even after 24 hours at room temperature with any of the compounds. Now boron trichloride is readily reduced by lithium aluminium hydride *in the presence of ether* to give diborane. In the absence of ether, reduction is difficult and the yield of diborane poor, suggesting that the ether is a necessary participant in the reduction (Paddock, *Nature*, 1951, **167**, 1070). However, in ethereal solution boron trichloride is present as the moderately stable etherate $Et_2\overset{+}{O}-\overset{-}{B}Cl_3$, and the reduction can be represented as $Et_2\overset{+}{O}-\overset{-}{B}Cl_3 \xrightarrow{LiAlH_4} Et_2\overset{+}{O}-\overset{-}{B}H_3$, followed by decomposition of the unstable borine etherate $2Et_2\overset{+}{O}-\overset{-}{B}H_3 \longrightarrow B_2H_6 + 2Et_2O$. This may explain why the reduction of boron trichloride in ethereal solution proceeds to virtual completion. But when boron trichloride is co-ordinated to a Group V trialkyl, solution in ether yields no etherate, *i.e.*, the ether does not displace the trialkyl donor molecule.

More important, a strong donor molecule M greatly reduces the reactivity of the boron-attached halogens in $\overset{+}{M}-\overset{-}{B}X_3$ compounds; *e.g.*, in boron trichloride or its etherate, chlorine atoms are readily replaceable by hydroxyl groups, by the action of water or alcohol; but these reagents have no action on boron trichloride–trimethylamine $Me_3\overset{+}{N}-\overset{-}{B}Cl_3$. The non-reactivity of $\overset{+}{M}-\overset{-}{B}Cl_3$ compounds towards lithium aluminium hydride in ethereal solution may thus be accounted for.

Experimental

The compounds described were prepared and studied in a vacuum apparatus as described by Stock ("The Hydrides of Boron and Silicon," Cornell, 1933) and by Sanderson ("Vacuum Manipulation of Volatile Compounds," Wiley, 1948). The two reactants were condensed in a tube (Sanderson, *op. cit.*), the latter was sealed off, and reaction allowed to proceed. The contents were then frozen in liquid nitrogen, the tube opened to the vacuum apparatus, and any non-condensable gas pumped off and transferred to a gas burette with a Töpler pump. Other volatile products of reaction were then removed and fractionated, and the amounts measured. The reaction tube was again sealed, transferred to a dry box, and opened to allow removal of the solid or liquid product for analysis or for study of reactions.

Analysis.—Where the trialkyl component of the compound was sufficiently volatile, the amounts of reactants and products could be determined and a material balance was obtained. With less volatile trialkyl components, analysis for boron and the donor atom was carried out, and this analysis was also made on the compounds formed with volatile trialkyls as a check. The molecular weight of each compound was determined by a cryoscopic method using a thermistor and benzene as solvent (Holliday and Sowler, *J.*, 1952, 11). Analysis for phosphorus was by fusion with sodium peroxide, precipitation of the resulting phosphate as ammonium phosphomolybdate, and alkalimetric titration of the latter. For arsenic, fusion with the peroxide was followed by acidification and reduction to the As(III) state with potassium iodide; the liberated iodine was boiled off, glycerol added to prevent decomposition of excess of iodide, and the neutral solution titrated with standard iodine. Boron analyses were by hydrolysis of the compound in a sealed tube, followed by titration of the liberated boric acid in presence of mannitol.

Vapour-pressure–Temperature Curves.—These were determined in an apparatus similar to that of Stock and Küss (*Ber.*, 1914, **47**, 3115). The products of thermal decomposition were analysed in the vacuum apparatus; methane and hydrogen mixtures were determined by combustion with oxygen over a platinum spiral attached to the Töpler pump gas burette; from the contraction in volume after combustion the relative amounts of methane and hydrogen were calculated.

Materials.—The diborane was obtained by reduction of boron trichloride (v. p. 3—4 mm. at −78°) with lithium aluminium hydride in ether (Finholt, Bond, and Schlesinger, *J. Amer. Chem. Soc.*, 1947, **69**, 1199). After fractionation in the vacuum apparatus it had v. p. 228 mm. at −112°; hydrogen was evolved on storage, and this was pumped off and the residue re-fractionated to give the same v. p. before use. In all reactions of diborane, a little hydrogen was produced, owing to surface reaction (Emeléus and Stone, *J.*, 1950, 2755). The Group V trialkyls were prepared by reaction of the appropriate trichloride in ether with the requisite Grignard reagent, followed by destructive distillation at 200° (for trimethyl- and triethyl-phosphine) or by hydrolysis (for the other trialkyls). The ethereal distillates or extracts were then shaken with a solution of silver iodide in potassium iodide to form the corresponding complexes (Mann, Wells, and Purdie, *J.*, 1937, 1828), and the latter were filtered off and dried (P_2O_5). The free trialkyl compounds were then regenerated by heating the complex in a tube attached to the vacuum system.

The following exemplify the methods used in studying the compounds listed in Table 1:

Preparation of trimethylphosphine–borine. 112·6N-c.c. (5·02 mmol.) of trimethylphosphine and 110·5N-c.c. (4·93 mmol.) of diborane were condensed in a reaction tube and sealed off from the vacuum line. The temperature was brought to ~20°, and the tube left for 24 hours to allow completion of the reaction. The tube was then cooled in liquid nitrogen and opened to the vacuum system, and the small amount of hydrogen pumped off and measured (0·12N-c.c.). Excess of diborane was then removed at −78° and unreacted trimethylphosphine was evaporated off as rapidly as possible at room temperature to prevent volatilisation of the addition

compound. 52·4N-c.c. of diborane were found to have reacted with 108·4N-c.c. of trimethylphosphine [Found: B, 11·6; P, 39·9%; P : B = 1·03 : 1; *M*, 91·4. $Me_3\overset{+}{P}-\overset{-}{B}H_3$ requires B, 12·0; P, 34·5%; *M*, 89·7].

Thermal decomposition of trimethylarsine–borine. 0·1059 G. (17·75N-c.c.) of the compound, heated at 120° for 3 hours, yielded 2·49N-c.c. of gas non-condensable at liquid-nitrogen temperature; on combustion with oxygen, it gave carbon dioxide, and the oxygen consumed corresponded to 2·25N-c.c. of hydrogen and 0·24N-c.c. of methane. A small amount of material volatile above −78° was also formed, and evolved hydrogen on storage, but after fractionation there was too little for identification.

Reaction with hydrogen chloride. Excess of hydrogen chloride was condensed on a small amount of the compound in a tube, which was sealed at liquid-nitrogen temperature; a vigorous reaction occurred on warming it to room temperature. After 24 hours, 0·0051 g. (0·85N-c.c.) of the compound reacted with 2·94N-c.c. of hydrogen chloride yielding 1·49N-c.c. of hydrogen; after 170 hours, 0·0323 g. (5·41N-c.c.) of product reacted with 18·6N-c.c. of hydrogen chloride, giving 13·1N-c.c. of hydrogen. No other volatile product was found. The acid left in the reaction tube was warmed gently to free it from any unchanged complex, and then had m. p. >170°. A specimen of trimethylarsine–boron trichloride, prepared by Phillips, Hunter, and Sutton's method (*loc. cit.*) (Found: Cl, 45·4. Calc. for $Me_3\overset{+}{As}-\overset{-}{B}Cl_3$: Cl, 44·9%), also had m. p. >170°. Addition of lithium aluminium hydride to this compound dissolved in ether gave no visible reaction, and no precipitate after 24 hours at room temperature. The lithium aluminium hydride was destroyed by careful addition of water and the ether layer rapidly separated, dried, evaporated, and extracted with benzene to remove any lithium chloride. The evaporated extract gave a solid, m. p. >170°.

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108. *Steroids. Part VI.* The Reduction of Ergosteryl-D Acetate 22 : 23-Dibromide.*

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Catalytic hydrogenation of ergosteryl-D acetate 22 : 23-dibromide (I; R = $C_9H_{17}Br_2$) in neutral medium gives 22 : 23-dibromoergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$, R′ = Ac) whereas in acetic acid the product is the $\Delta^{8(14)}$-compound (III; R = $C_9H_{17}Br_2$, R′ = Ac), also obtained by rearrangement of the Δ^7-isomer on a platinum catalyst saturated with hydrogen. Debromination of the $\Delta^{8(14)}$-compound, which is also obtained by hydrogenolysis of the 9α : 11α-epoxide (IV; R = $C_9H_{17}Br_2$) and of 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one (V; R = $C_9H_{17}Br_2$), gives ergosta-8(14) : 22-dien-3β-yl acetate (III; R = C_9H_{17}, R′ = Ac). Treatment of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate with hydrogen chloride gives an inseparable mixture of 22 : 23-dibromoergost-14-en-3β-yl acetate and the $\Delta^{8(14)}$-isomer. Catalytic hydrogenation of this mixture followed by removal of unsaturated material gives 22 : 23-dibromoergostan-3β-yl acetate and thence ergost-22-en-3β-yl acetate.

IN Part II of this series (*J.*, 1952, 2901) the preparation of 22 : 23-dibromoergosta-7 : 9(11)-dien-3β-yl acetate (ergosteryl-D acetate 22 : 23-dibromide) (I; R = $C_9H_{17}Br_2$, R′ = Ac) is described and in Parts III and V (*J.*, 1952, 3410, 4874) a preliminary account is given of its oxidation. Ergosteryl-D acetate 22 : 23-dibromide offers some advantage over ergosteryl-D acetate (I; R = C_9H_{17}, R′ = Ac) as a starting point for the synthesis of 11-keto-steroids since nuclear oxidation is more efficiently effected in the former than in the latter, presumably because of partial attack at the side-chain ethylenic linkage. The present paper describes the catalytic reduction of ergosteryl-D acetate 22 : 23-dibromide. The side-chain halogens proved to be a satisfactory protection of the 22 : 23-double linkage of

* Part V, *J.*, 1952, 4874.

ergosteryl-D acetate under the hydrogenation conditions used, and, together with the easy regeneration of the ethylenic linkage by zinc dust, has led to efficient methods for the preparation of ergosta-8(14) : 22-dien-3β-ol and ergost-22-en-3β-ol. Of these compounds, the former has been described by Laubach and Brunings (*J. Amer. Chem. Soc.*, 1952, **74**, 705) since this work was completed; they prepared it by hydrogenation of ergosteryl-β_2 acetate [ergosta-6 : 8(14) : 22-trien-3β-yl acetate] in a neutral solvent over Raney nickel. Ergost-22-en-3β-ol has been obtained by Barton, Cox, and Holness (*J.*, 1949, 1771) by partial hydrogenation of *iso*ergosterone in neutral solution to ergost-22-en-3-one followed by reduction of the latter with sodium and propanol.

Hydrogenation of ergosteryl-D acetate 22 : 23-dibromide in ethyl acetate over platinum gives 22 : 23-dibromoergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$, R′ = Ac) which was characterised by hydrolysis to the alcohol and as the derived benzoate. The molecular-rotation data (Table 1) support the structure allocated to 22 : 23-dibromoergost-7-en-3β-ol. Furthermore the observed changes in molecular rotation accompanying saturation of the double bond (comparison with 22 : 23-dibromoergostan-3β-ol, its acetate and benzoate) are in good agreement with values for the saturation of comparable stenols (Barton, *J.*, 1946, 512; Barton and Cox, *J.*, 1948, 1354). The structure allocated to 22 : 23-dibromoergost-7-en-3β-yl acetate was confirmed by its conversion in high yield into ergosta-7 : 22-dien-3β-yl acetate (5-dihydroergosteryl acetate) (II; R = C_9H_{17}, R′ = Ac) by treatment with zinc dust.

Hydrogenation of ergosteryl-D acetate 22 : 23-dibromide in acetic acid over platinum gives 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (III; R = $C_9H_{17}Br_2$, R′ = Ac) characterised as in the case of the Δ^7-isomer. Furthermore, shaking 22 : 23-dibromoergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$, R′ = Ac) in acetic acid solution with a platinum catalyst saturated with hydrogen isomerised it to 22 : 23-dibromoergost-8(14)-en-3β-yl acetate. The location of the double bond in these compounds follows from well-established considerations (see Fieser and Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., 1949). Thus the molecular-rotation changes on acetylation (Δ_1) and benzoylation (Δ_2) of the alcohol are in good agreement with representative values for other 5α-st-8(14)-en-3β-ols and the ultra-violet absorption spectrum of the compound agrees with that expected for an 8(14)-stenol (Bladen, Henbest, and Woods, *Chem. and Ind.*, 1951, 866; Halsall, *ibid.*, p. 867). However, although the molecular-rotation changes on acetylation and benzoylation of 22 : 23-dibromoergost-8(14)-en-3β-ol are normal, the

TABLE 1.

	$[M]_D$				
	Alcohol	Acetate	Benzoate	Δ_1	Δ_2
22 : 23-Dibromoergostan-3β-ol	+42°	+12°	+40°	−30° (−34°)	−2° (+2°)
22 : 23-Dibromoergost-7-en-3β-ol ...	−47	−42	−26	+5 (−6)	+21 (+30)
Δ (Saturation of ⊢)	+89 (+77)	+54 (+57)	+66 (+64)	—	—
22 : 23-Dibromoergost-8(14)-en-3β-ol	+73	+27	+20	−46 (−40)	−53 (−42)
Δ (Saturation of ⊢)	−31 (+9)	−15 (+14)	+20 (+53)	—	—

Standard values, from Barton, *J.*, 1945, 813; 1946, 512, are given in parentheses.

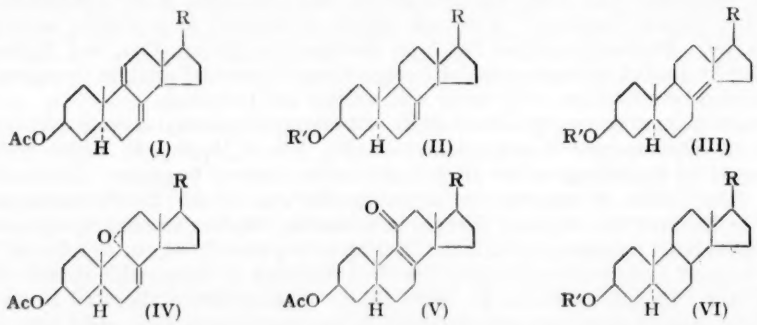
Δ-values for saturation of the double bond are only in fair agreement with standard values for 8(14)-stenols. This indicates some degree of vicinal effect of the side chain (cf. Mancera, Barton, Rosenkranz, and Djerassi, *J.*, 1952, 1021).

Debromination of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate with zinc gives ergosta-8(14) : 22-dien-3β-yl acetate (III; R = C_9H_{17}, R′ = Ac), hydrolysed by alkali to the alcohol and hydrogenated in ethyl acetate or acetic acid over platinum to ergost-8(14)-en-3β-yl acetate (III; R = C_9H_{19}, R′ = Ac) (α-ergostenyl acetate).

A study of the catalytic reduction products of two oxidation products of ergosteryl-D acetate 22 : 23-dibromide, namely, 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (IV; R = $C_9H_{17}Br_2$) and 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one (V; R = $C_9H_{17}Br_2$) (Part III, *loc. cit.*) was included in this investigation. In acetic acid solution over a platinum catalyst both compounds suffered hydrogenolysis with the formation of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (III; R = $C_9H_{17}Br_2$, R′ = Ac). 3β-Acetoxy-22 : 23-

dibromoergost-8-en-11-one was recovered unchanged after being shaken with hydrogen in ethyl acetate solution over platinum catalyst or in acetic acid solution over palladium black.

Treatment of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate or benzoate with dry hydrogen chloride gave mixed crystals which could not be resolved by crystallisation. De-



bromination of the acetate dibromide mixed crystal gave "β"-dihydroergosteryl acetate, characterised by the preparation of the corresponding alcohol and benzoate. "β"-Dihydroergosteryl acetate was shown by Barton, Cox, and Holness (*J.*, **1949**, **1771**) to be an inseparable equimolar mixture of ergosta-8(14) : 22-dien-3β-yl acetate and ergosta-14 : 22-dien-3β-yl acetate. The product obtained by isomerisation of 22 : 23-dibromoergost-8(14)-en-3-βyl acetate is therefore a mixture of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate and 22 : 23-dibromoergost-14-en-3β-yl acetate, and, since it gives "β"-dihydroergosteryl acetate in nearly quantitative yield, it is inferred that it likewise is an equimolar mixture. The molecular rotations of 22 : 23-dibromoergost-14-en-3β-ol and its derivatives, calculated from the values for 22 : 23-dibromoergost-8(14)-en-3β-ol and those of the mixed crystals (22 : 23-dibromoergost-8(14)-stenol and 22 : 23-dibromoergost-14-stenol) are shown in Table 2. Although the Δ values for acetylation and benzoylation of 22 : 23-dibromoergost-14-en-3β-ol are in reasonable agreement with standard values for Δ^{14}-stenols, the changes in molecular rotation accompanying saturation of the double bond of this compound and its derivatives (comparison with corresponding derivatives of 22 : 23-dibromoergostan-3β-ol) are anomalous, in this respect resembling 22*a-allo*spirost-8(14)-en-3β-ol in which a strong vicinal effect of the sapogenin side chain was also observed (Mancera, Barton, Rosenkranz, and Djerassi, *loc. cit.*). Summarising, the dibrominated side-chain exerts a profound vicinal effect upon the 14(15)-, a less pronounced effect upon the 8(14)-, and no effect upon a 7(8)-ethylenic linkage.

A preparation of 22 : 23-dibromoergostan-3β-yl acetate (VI; R = $C_9H_{17}Br_2$, R' = Ac) was achieved by isomerisation of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate with dry

TABLE 2.

	$[M]_D$				
	Alcohol	Acetate	Benzoate	Δ_1	Δ_2
22 : 23-Dibromoergost-8(14)-en-3β-ol	+73°	+27°	+20°	—	—
[22 : 23-Dibromoergost-8(14)-en-3β-ol + 22 : 23-Dibromoergost-14-en-3β-ol (1 : 1)]	+165	+126	+139	—	—
22 : 23-Dibromoergost-14-en-3β-ol	+257	+225	+258	−32° (−35°)	+1° (+30°)
22 : 23-Dibromoergostan-3β-ol ...	+42	+12	+40	—	—
Δ (Saturation of ⊢)	−215 (−24)	−213 (−20)	−218 (−59)	—	—

hydrogen chloride, hydrogenation of the product, and removal of unsaturated material by Anderson and Nabenhauer's method (*J. Amer. Chem. Soc.*, 1924, **46**, 1951). Attempts to improve the preparation by reduction of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate in the presence of hydrochloric acid were not successful. Debromination of 22 : 23-dibromoergostanyl acetate gave ergost-22-en-3β-yl acetate (VI; R = C_9H_{17}, R' = Ac), characterised by hydrolysis to the alcohol.

Experimental

M. p.s are corrected. Specific rotations were measured in chloroform solution in a 1-dm. tube at 18—20°. Ultra-violet absorption spectra were measured in absolute ethanol solution with a Unicam SP.500 spectrophotometer. " Working up in the usual way " means removal of catalyst, concentration under reduced pressure, addition of water, extraction with ether, washing of the extract with dilute sodium carbonate solution and water, drying (Na_2SO_4), and evaporation under reduced pressure.

22 : 23-*Dibromoergost*-8(14)-*en*-3β-*yl Acetate*.—(*a*) A solution of ergosteryl-D acetate 22 : 23-dibromide (500 mg.) in glacial acetic acid (250 c.c.) was added to a suspension of freshly reduced platinum (from 200 mg. of platinum oxide) in acetic acid (15 c.c.), and the mixture shaken with hydrogen for 20 hours at room temperature. Working up in the usual way gave 22 : 23-*dibromoergost*-8(14)-*en*-3β-*yl acetate* which separates from methanol–chloroform as elongated plates, m. p. 192—193° (400 mg.), $[\alpha]_D$ +5°, +4·5° (*c*, 2·0, 7·0). After chromatography of a specimen on alumina followed by crystallisation from methanol–chloroform it had $[\alpha]_D$ +4° (*c*, 2·5) (Found: C, 60·1; H, 8·3. $C_{30}H_{48}O_2Br_2$ requires C, 60·0; H, 8·0%). Light absorption: ε_{2100} 8000, ε_{2150} 7500, ε_{2200} 5600, ε_{2230} 1400. It gives a deep yellow colour with tetranitromethane in chloroform. The same product was obtained when chloroform–glacial acetic acid (1 : 9 parts) was used as solvent for the hydrogenation.

(*b*) A solution of 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one (500 mg.) in glacial acetic acid (100 c.c.) was shaken with hydrogen over pre-reduced platinum oxide (200 mg.) for 10 hours. Working up in the usual way gave 22 : 23-dibromoergost-8(14)-en-3β-yl acetate as plates (from methanol–chloroform), m. p. 189—191° (250 mg.), $[\alpha]_D$ +3° (*c*, 1·0), undepressed in m. p. when mixed with the specimen described under (*a*) (Found: C, 60·2; H, 8·4%).

(*c*) A solution of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (m. p. 216—218°; 500 mg.) in glacial acetic acid (80 c.c.) was shaken with hydrogen for 4 hours over platinum (from 100 mg. of PtO_2). Working up in the usual way gave 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (450 mg.) as plates (from methanol–chloroform), m. p. 191—192°, $[\alpha]_D$ +3° (*c*, 1·1), undepressed in m. p. when mixed with the specimen described under (*a*) (Found: C, 60·0; H, 8·1%).

22 : 23-*Dibromoergost*-8(14)-*en*-3β-*ol*.—A solution of the acetate (250 mg.) in benzene (10 c.c.) and methanolic potassium hydroxide (40 c.c.; 1%) was refluxed for 1 hour. The solution was diluted with water and extracted with ether. Removal of ether gave a solid which crystallised from methanol–chloroform to give 22 : 23-*dibromoergost*-8(14)-*en*-3β-*ol* as plates, m. p. 213—214° (200 mg.), $[\alpha]_D$ +13 (*c*, 1·6) (Found: C, 60·3; H, 8·6. $C_{28}H_{46}OBr_2$ requires C, 60·2; H, 8·3%).

The alcohol in pyridine and benzoyl chloride was heated at 100° for 1 hour and kept at room temperature for 2 hours. Crystallisation of the product from chloroform–methanol gave the *benzoate* as plates, m. p. 242—243°, $[\alpha]_D$ +3° (*c*, 5·0, 4·5) (Found: C, 63·4; H, 7·8. $C_{35}H_{50}O_2Br_2$ requires C, 63·4; H, 7·6%).

22 : 23-*Dibromoergost*-7-*en*-3β-*yl Acetate*.—A solution of ergosteryl-D acetate 22 : 23-dibromide (0·5 g.) in ethyl acetate (100 c.c.) was shaken with hydrogen over pre-reduced platinum oxide (100 mg.) for 14 hours. Working up in the usual way gave 22 : 23-*dibromoergost*-7-*en*-3β-*yl acetate* (*5-dihydroergosteryl acetate* 22 : 23-*dibromide*) as needles (from methanol–ethyl acetate), m. p. 224° (decomp.) (0·4 g.), $[\alpha]_D$ −7° (*c*, 2·0, 1·4) (Found: C, 60·3; H, 8·2%). Light absorption: ε_{2100} 5000, ε_{2150} 3620, ε_{2200} 1700. It gives a yellow colour with tetranitromethane in chloroform.

22 : 23-*Dibromoergost*-7-*en*-3β-*ol*.—A solution of 22 : 23-dibromoergost-7-en-3β-yl acetate (200 gm.) in benzene (15 c.c.) and methanolic potassium hydroxide (25 c.c.; 2%) was refluxed for 1 hour, concentrated, and diluted with water. Isolation by means of ether, followed by crystallisation from methanol, gave 22 : 23-*dibromoergost*-7-*en*-3β-*ol* as plates, m. p. 222—223° (165 mg.), $[\alpha]_D$ −8° (*c*, 1·3) (Found: C, 59·1; H, 8·6. $C_{28}H_{46}OBr_2,CH_3{\cdot}OH$ requires C, 59·0; H, 8·5%). Reacetylation (acetic anhydride–pyridine) gave the parent acetate as needles (from methanol–chloroform), m. p. 224°, $[\alpha]_D$ −6° (*c*, 1·5). The *benzoate*, prepared in the usual way, separates from methanol–chloroform as needles, m. p. 205° (decomp.), $[\alpha]_D$ −4° (*c*, 4·0) (Found: C, 63·4; H, 7·8%).

Isomerisation of 22 : 23-*Dibromoergost*-7-*en*-3β-*yl Acetate*.—A solution of this acetate (500 mg.) in acetic acid (300 c.c.) was shaken with a platinum catalyst and hydrogen for 4 hours. Working up in the usual way gave 22 : 23-dibromoergost-8(14)-en-3β-yl acetate as plates (from methanol–chloroform), m. p. and mixed m. p. 190° (400 mg.), $[\alpha]_D$ +4° (*c*, 3·0).

Ergosta-7 : 22-dien-3β-*yl Acetate*.—A solution of 22 : 23-dibromoergost-7-en-3β-yl acetate (250 mg.) in ether–ethanol (60 c.c.; 1 : 1) was refluxed with zinc dust (1·5 g.) for 2 hours. The solution was filtered, concentrated, and diluted with water. Isolation by means of ether gave ergosta-7 : 22-dien-3β-yl acetate as plates (from methanol–chloroform), m. p. 182—183° (150 mg.), $[\alpha]_D$ −20° (*c*, 1·2), undepressed in m. p. when mixed with an authentic sample, m. p. 182°, $[\alpha]_D$ −20° (Found : C, 82·1; H, 11·1. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%).

Ergosta-8(14) : 22-*dien*-3β-*yl Acetate*.—A solution of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (m. p. 191—193°; 200 mg.) in ether–methanol (50 c.c.; 1 : 2) was refluxed with zinc dust (2 g.) added portionwise during 3 hours. The solution was filtered, concentrated, and diluted with water. Isolation by means of ether gave ergosta-8(14) : 22-dien-3β-yl acetate, as plates (from methanol), m. p. 122—123·5° (120 mg.), $[\alpha]_D$ −25° (*c*, 1·1) (Found : C, 81·5; H, 11·2. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%). Light absorption : ε_{2120} 8000, ε_{2150} 7000, ε_{2200} 4900. It gives a deep yellow colour with tetranitromethane in chloroform. Laubach and Brunings (*loc. cit.*) give m. p. 122·6—124·0°, $[\alpha]_D$ −26·5°.

Ergosta-8(14) : 22-*dien*-3β-*yl Benzoate*.—A solution of 22 : 23-dibromoergost-8(14)-en-3β-yl benzoate (500 mg.) in pyridine (30 c.c.) containing water (3 drops) was heated with zinc dust (4 g.) for 3 hours on the steam-bath. The mixture was filtered, and the filtrate concentrated under reduced pressure and diluted with water. Working up using ether gave *ergosta*-8(14) : 22-*dien*-3β-*yl benzoate* (380 mg.) as flat needles (from methanol–chloroform), m. p. 126—127°, $[\alpha]_D$ −24°, −23° (*c*, 4·1, 4·0) (Found : C, 83·8; H, 10·2. $C_{35}H_{50}O_2$ requires C, 83·6; H 10·0%). It gives a deep yellow colour with tetranitromethane in chloroform.

Ergosta-8(14) : 22-*dien*-3β-*ol*.—A solution of ergosta-8(14) : 22-dien-3β-yl acetate (60 mg.) in methanolic potassium hydroxide (20 c.c.; 3%) was refluxed for 2 hours, then concentrated and diluted with water. Isolation by means of ether gave *ergosta*-8(14) : 22-*dien*-3β-*ol* which crystallised from methanol or acetone as elongated plates m. p. 126—127° (40 mg.), $[\alpha]_D$ −19°, −20° (*c*, 1·5, 1·0) (Found : C, 84·2; H, 11·8. $C_{28}H_{46}O$ requires C, 84·35; H, 11·6%).

Acetylation (acetic anhydride–pyridine) gave ergosta-8(14) : 22-dien-3β-yl acetate as plates (from methanol), m. p. 123—124° (25 mg.), $[\alpha]_D$ −27° (*c*, 1·3).

Ergost-8(14)-*en*-3β-*yl Acetate*.—A solution of ergosta-8(14) : 22-dien-3β-yl acetate (100 mg.) in ethyl acetate (60 c.c.) was shaken with hydrogen over freshly reduced platinum oxide catalyst for 5 hours. The filtered reaction mixture was concentrated, giving plates (80 mg.) which on recrystallisation from methanol gave ergost-8(14)-en-3β-yl acetate as plates, $[\alpha]_D$ +4° (*c*, 2·0), m. p. 109—110°, either alone or mixed with an authentic sample, m. p. 108—109°, $[\alpha]_D$ +3°, prepared by hydrogenation of ergosteryl-D acetate in glacial acetic acid (Found : C, 81·2; H, 11·4. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). Light absorption : ε_{2100} 7000, ε_{2150} 6400, ε_{2200} 4600. It gives a yellow colour with tetranitromethane in chloroform. The same product in similar yield was obtained by using chloroform or glacial acetic acid as solvent for the hydrogenation.

Treatment of 22 : 23-*Dibromoergost*-8(14)-*en*-3β-*yl Acetate with Hydrogen Chloride*.—Dry hydrogen chloride was passed into a solution of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (1 g.) in dry chloroform (20 c.c.) for 90 minutes at 0°. The solvent was removed under reduced pressure and the solid crystallised from methanol–chloroform, to give plates, m. p. 225—226° (decomp.) (600 mg.), $[\alpha]_D$ +21° (*c*, 2·0) (Found : C, 60·1; H, 8·0. $C_{30}H_{48}O_2Br_2$ requires C, 60·0; H, 8·0%). Light absorption : ε_{2060} 4000, ε_{2100} 3000, ε_{2150} 1250, ε_{2200} 620. The *compound* gives a yellow colour with tetranitromethane in chloroform.

Hydrolysis of this acetate (300 mg.) in benzene (20 c.c.) by refluxing with methanolic potassium hydroxide (2%; 45 c.c.) for 2 hours gave the corresponding *alcohol* (240 mg.; m. p. 216—219°) which after three crystallisations from methanol separated as plates, m. p. 219—220°, $[\alpha]_D$ +29° (*c*, 1·9) (Found : C, 58·7; H, 8·7. $C_{28}H_{46}OBr_2,CH_3{\cdot}OH$ requires C, 59·0; H, 8·5%).

Acetylation of the alcohol (pyridine–acetic anhydride) gave the acetate which separated from methanol–chloroform as plates, $[\alpha]_D$ +22° (*c*, 1·3°), m. p. 223—225 (decomp.) alone or mixed with the acetate described above.

Refluxing the acetate (300 mg.) in ether–ethanol (40 c.c.; 1 : 1) with zinc dust (1 g.) gave " β "-dihydroergosteryl acetate which separated from methanol–chloroform as needles, m. p. 106—107° (200 mg.), $[\alpha]_D$ −18° (*c*, 1·6) (Found : C, 82·1; H, 11·4. Calc. for $C_{30}H_{48}O_2$: C, 81·8; H, 11·0%). Light absorption : ε_{2100} 2550, ε_{2150} 730. It gives a deep yellow colour with tetranitromethane in chloroform. Barton, Cox, and Holness (*loc. cit.*) give m. p. 104·5°, $[\alpha]_D$ −17°, for " β "-dihydroergosteryl acetate.

Hydrolysis of the acetate with methanolic potassium hydroxide (2%) followed by crystallisation of the product from methanol–chloroform gave " β "-dihydroergosterol as plates, m. p.

115—116°, $[\alpha]_D$ −11° (*c*, 1·2). Barton, Cox, and Holness (*loc. cit.*) give m. p. 116°, $[\alpha]_D$ −9°, for this compound.

Benzoylation of the alcohol by the usual procedure gave the benzoate (plates from methanol–chloroform), m. p. 118°, $[\alpha]_D$ −9·5° (*c*, 1·7) (lit., m. p. 116°, $[\alpha]_D$ −8°).

Treatment of 22 : 23-*Dibromoergost*-8(14)-*en*-3β-*yl Benzoate with Hydrogen Chloride.*—Dry hydrogen chloride was passed through a solution of 22 : 23-dibromoergost-8(14)-en-3β-yl benzoate (1 g.) in dry chloroform (30 c.c.) for 2 hours at 0°. Working up gave a product which separated from methanol–chloroform in plates (0·86 g.), m. p. 229—231°, $[\alpha]_D$ +21° (*c*, 2·0). Four further crystallisations from the same solvent gave mixed crystals, m. p. 232° (decomp.), $[\alpha]_D$ +21°, +20° (*c*, 2·4, 4·0) (Found: C, 63·3; H, 7·8. $C_{35}H_{50}O_2Br_2$ requires C, 63·4; H, 7·6%).

The benzoate (75 mg.) in refluxing benzene (25 c.c.) and methanolic potassium hydroxide (3%; 25 c.c.) (4 hours) gave the alcohol as plates (55 mg.) (from methanol), m. p. 219—220°, $[\alpha]_D$ +29° (*c*, 1·3). The alcohol was undepressed in m. p. when mixed with the alcohol obtained by isomerisation of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate followed by hydrolysis.

22 : 23-*Dibromoergostan*-3β-*yl Acetate.*—Dry hydrogen chloride was passed through a solution of 22 : 23-dibromoergost-8(14)-en-3β-yl acetate (0·8 g.) in chloroform (25 c.c.) for 2 hours at 0°. After the removal of the solvent under reduced pressure, a solution of the solid in ether (100 c.c.) and ethyl acetate (100 c.c.) was shaken with hydrogen over platinum (from 200 mg. of PtO_2) for 20 hours. Working up in the usual way gave a solid which was dissolved in carbon tetrachloride (30 c.c.). Acetic anhydride (10 c.c.) and concentrated sulphuric acid (10 c.c.) were added slowly with shaking and cooling, and the mixture shaken for 5 minutes. Water (10 c.c.) was added and the mixture extracted with carbon tetrachloride. The combined extracts were washed with water, sodium hydrogen carbonate, water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a pale yellow solid (470 mg.) which crystallised from methanol–chloroform, to give 22 : 23-dibromoergostan-3β-yl acetate (250 mg.) as plates, m. p. 242—243° (decomp.), $[\alpha]_D$ +3°, +2·7° (*c*, 2·2, 3·0) (Found: C, 60·4; H, 8·6. Calc. for $C_{30}H_{50}O_2Br_2$: C, 59·9; H, 8·4%). It does not give a colour with tetranitromethane in chloroform and does not show absorption of high intensity above 2000 Å. Barton, Cox, and Holness (*loc. cit.*) give decomp. *ca.* 226° for this compound.

22 : 23-*Dibromoergostan*-3β-*ol.*—A solution of 22 : 23-dibromoergostan-3β-yl acetate (115 mg.) in benzene (20 c.c.) and methanolic potassium hydroxide (20 c.c.; 2%) was heated under reflux for 1 hour. Isolation by means of ether gave 22 : 23-*dibromoergostan*-3β-*ol* which crystallised from chloroform as plates, m. p. 239—240° (85 mg.), $[\alpha]_D$ +7° (*c*, 1·45) (Found: C, 58·4; H, 8·9. $C_{28}H_{48}OBr_2,CH_3{\cdot}OH$ requires C, 58·8; H, 8·9%).

22 : 23-*Dibromoergostan*-3β-*yl benzoate*, prepared in the usual way, crystallised from methanol–chloroform as plates, m. p. 218°, $[\alpha]_D$ +6° (*c*, 2·5) (Found: C, 63·6; H, 8·2. $C_{35}H_{52}O_2Br_2$ requires C, 63·3; H, 7·9%).

Ergost-22-*en*-3β-*yl Acetate.*—A solution of 22 : 23-dibromoergostan-3β-yl acetate (150 mg.) in ether–ethanol (75 c.c.; 1 : 1) was refluxed with zinc dust (1 g.) added portionwise during 2 hours. Working up in the usual way gave ergost-22-en-3β-yl acetate which crystallised from methanol–chloroform in plates (60 mg.), m. p. 157°, $[\alpha]_D$ −20°, −18° (*c*, 1·3, 1·4) (Found: C, 81·0; H, 11·4. Calc. for $C_{30}H_{50}O_2$: C, 81·4; H, 11·4%). Barton, Cox, and Holness (*loc. cit.*) give m. p. 155·5°, $[\alpha]_D$ −17°, for this compound.

Ergost-22-*en*-3β-*ol.*—A solution of ergost-22-en-3β-yl acetate (40 mg.) in benzene (2 c.c.) and methanolic potassium hydroxide (2 c.c.; 2%) was heated under reflux for 1 hour. Isolation by means of ether gave ergost-22-en-3β-ol which crystallised from methanol–chloroform as plates, m. p. 153—154° (25 mg.), $[\alpha]_D$ −10° (*c*, 1·3) (Found: C, 81·9; H, 12·2. Calc. for $C_{28}H_{48}O,\frac{1}{2}H_2O$: C, 82·1; H, 12·1%).

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109. *Steroids. Part IV.* Solvolysis of* epi*Cholesteryl Toluene*-p-*sulphonate and other Steroid Toluene*-p-*sulphonates.*

By D. D. Evans and C. W. Shoppee.

Acetolysis of *epi*cholesteryl toluene-*p*-sulphonate leads exclusively to cholesta-3 : 5-diene, but methanolysis furnishes in addition to this hydrocarbon two isomeric methoxy-compounds for which structures are suggested. The reactions of the epimeric coprostanyl toluene-*p*-sulphonates have been examined; on solvolysis the *epi*coprostanyl derivative undergoes substitution whereas the epimeride undergoes elimination.

Solvolysis of 3β-substituted Δ^5-steroids may lead either to replacement of the 3β-substituent with complete retention of configuration (Shoppee, *J.*, 1946, 1147) or to 6β-substituted 3 : 5-*cyclo*steroids with inversion of configuration at $C_{(3)}$ (Shoppee and Summers, *J.*, 1952, 3361). In 1948 an examination of the solvolysis of 3α-substituted Δ^5-steroids was commenced with *epi*cholesteryl toluene-*p*-sulphonate, methanesulphonate and, it was hoped, the chloride. We recently learnt that a similar investigation has been carried out with the toluene-*p*-sulphonate independently by Professor Hans Schmid of the University of Zurich. This account of our results is presented by agreement with Professor Schmid, who is publishing his results simultaneously in Switzerland.

Notwithstanding the presence of an adjacent unsaturated linking which confers trigonal symmetry on $C_{(5)}$ and $C_{(6)}$, ring A in Δ^5-steroids forms a slightly distorted chair somewhat inclined to the general plane of the ring system; paradoxically the inclusion of a 5 : 6-double bond deforms rather than flattens the ring system. The 3β-hydroxyl group of the sterols therefore possesses the equatorial conformation. The geometry of the system is thus favourable to interaction between $C_{(5)}$ and the α-face of $C_{(3)}$ (cf. Roberts, Bennett, and Armstrong, *J. Amer. Chem. Soc.*, 1950, **72**, 3329), and unfavourable to ionic 1 : 2-elimination reactions involving the 3β-substituent and requiring a *trans*-arrangement of the groups eliminated, whilst homogeneous unimolecular † thermal 1 : 2-elimination reactions involving the 3β-substituent and requiring a *cis*-disposition of the groups eliminated [3β-X(equatorial)/4α- or 2α-H(polar)] (cf. Bartow, *J.*, 1949, 2174) should proceed with some difficulty. It is consistent that reactions leading from cholesterol to cholesta-3 : 5-diene generally require elevated temperatures, *e.g.*, dehydration with copper sulphate at 200°, pyrolysis of the methyl xanthate at 200—205°, and decomposition of potassium cholesteryl sulphate in decyl alcohol–sodium decyloxide at 160—180°. It is possible however that in the last-named case an ionic mechanism supervenes in view of the strength of sulphuric acid.

The 3α-hydroxyl group in *epi*cholesterol (I*a*) possesses the polar conformation. The geometry of the system is now favourable to ionic 1 : 2-elimination reactions [3α-OH(polar)/4β- or 2β-H(polar)], but unfavourable to thermal elimination reactions and to interaction between $C_{(5)}$ and the β-face of $C_{(3)}$. We have found that simple chromatography of *epi*cholesteryl toluene-*p*-sulphonate in pentane on neutral aluminium oxide furnishes cholesta-3 : 5-diene in 94% yield, so that 1 : 2-elimination occurs with extreme ease. Nevertheless an examination of the methanolysis and acetolysis of *epi*cholesteryl toluene-*p*-sulphonate (I*b*), methanesulphonate (I*c*), and chloride (I*d*) was undertaken in the hope that, despite the ease of ionic elimination [mechanism *E*2] or of possible internal depolarisation of the cation (II) [mechanism *E*1] to yield cholesta-3 : 5-diene, rearrangement of the cation (II) might occur with formation of 6-substituted derivatives of 3 : 5-*cyclo*coprostane (III). It was realised that alternatively the cation (II) might undergo Wagner change leading to 2- or 4-substituted cholest-5-enes (IV), or, after triad change, to 6-substituted cholest-4-enes (V).

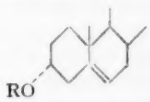
The *epi*cholesterol derivatives (I*b* and *c*) were prepared in good yield by use of the appropriate acid chloride in pyridine ‡ at 0—15°; both compounds give red colours on

* Part III, *J.*, 1952, 2528.

† In the sense in which this term is used in regard to gas-phase reactions.

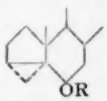
‡ All attempts directly to convert *epi*cholesterol into *epi*cholesteryl chloride failed, giving cholesta-3 : 5-diene as the sole crystalline product; the chloride was obtained subsequently by an indirect method (Shoppee and Summers, *J.*, 1952, 1790).

melting (also in nitrogen or in a vacuum), which are probably due to halochromic salts formed as the result of decomposition to cholesta-3 : 5-diene and the appropriate sulphonic acid. Although (I*b*) is converted into cholesta-3 : 5-diene by neutralised aluminium oxide at 20°, it gives the Rosenheim test only after an appreciable induction period. Acetolysis of (I*b*, *c*, or *d*) with potassium acetate–acetic acid or with silver acetate–acetic acid gives 92—99% of cholesta-3 : 5-diene. Clearly 1 : 2-ionic elimination proceeds, as expected, with great ease.

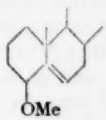


(I*a*; R = H) (I*b*; R = *p*-$C_6H_4Me{\cdot}SO_3$) (I*c*; R = $Me{\cdot}SO_3$) (I*d*; Cl for RO)

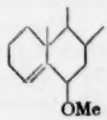
(II)



(III)



(IV)



(V)

Methanolysis of the toluene-*p*-sulphonate (I*b*) gave cholesta-3 : 5-diene (76%) and a methyl ether, m. p. 96°, $[\alpha]_D$ +82°, provisionally regarded as 6β-methoxycholest-4-ene (V) (7% yield). Methanolysis in the presence of potassium acetate afforded cholesta-3 : 5-diene (56, 57%), the methyl ether (V) (11, 13%), and an isomeric methyl ether, m. p. 66°, $[\alpha]_D$ −73°, provisionally regarded as 4β-methoxycholest-5-ene (IV) (19, 23%). Both methyl ethers give a positive Rosenheim test and a *pale* yellow colour (as also does pure 3 : 5-*cyclo*cholestane) with tetranitromethane–chloroform.

At first the two isomeric ethers were regarded as epimeric 6-methoxy-3 : 5-*cyclo*coprostanes (III); by treatment with hydrochloric acid–acetic acid at 20° both furnished cholesta-3 : 5-diene. Their infra-red spectra, determined by Dr. S. F. D. Orr of the Chester Beatty Research Institute, by examination of the solids in Nujol on a Perkin-Elmer instrument showed, in addition to the C–O–Me stretching vibration at 1094—1097 cm.$^{-1}$ (cf. Josien, Fuson, and Cary, *J. Amer. Chem. Soc.*, 1951, **73**, 4445), bands in the 850—910-cm.$^{-1}$ region and a rather weak band at 1019 ± 5 cm.$^{-1}$ where a *cyclo*propane ring structure might be expected to absorb (cf. Barton, *J.*, 1951, 1444). The spectra of *epi*cholesteryl methyl ether and 3β-methoxycoprostane show intense bands at 1097 and 1094 cm.$^{-1}$ respectively, and weak bands at 1026 and 1022 cm.$^{-1}$ respectively, but are noticeably free from bands in the 850—910-cm.$^{-1}$ region. On the other hand, the spectra of the epimeric ethers show a band at 812—815 cm.$^{-1}$, which also appears, slightly displaced, at 822 cm.$^{-1}$, in the spectrum of *epi*cholesteryl methyl ether but not in that of 3β-methoxycoprostane; this may be identified with the δ(CH) vibration in $-CH{=}C<$ (Günthard and Ruzicka, *Helv. Chim. Acta*, 1948, **31**, 642) and suggests the presence of an ethylenic linkage.*

Examination of the ultra-violet spectra of the epimeric ethers disclosed some selective absorption in the 205—215-mμ region, where 3 : 5-*cyclo*cholestane does not absorb and saturated steroids are practically transparent. The values of the molecular extinction coefficients for various cholestenes and the two isomeric ethers are as follows (cf. Bladon, Henbest, and Wood, *Chem. and Ind.*, 1951, 866) :

λ (mμ)	Cholest-2-ene	Cholest-3-ene	Cholest-4-ene	Cholest-5-ene	Ether (IV ?), m. p. 66°	Ether (V ?), m. p. 96°
205	400	1700	3900	3700	2220	2870
210	200	650	3000	2700	850	960
215	—	200	1500	1400	390	300
220	—	—	850	700	280	160

Measured in ethanol on a Unicam instrument with corrected scale.

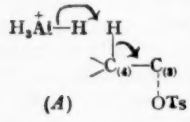
These figures show the presence of an ethylenic linkage in both ethers but do not differentiate clearly between the types CHR=CHR (Δ^2, Δ^3) and $CHR{=}CR_2$ (Δ^4, Δ^5). The less intense absorption observed in the two ethers, compared with chloest-4-ene and cholest-5-ene, may be due to the presence of a methoxy-group on the carbon atom adjacent, and *cis* rather than *trans*, to a double bond (cf. IV, V), since, although cholest-4-ene-3α- and 3β-

* The infra-red spectra of the epimeric ethers, kindly furnished by Professor Schmid for comparison, extend to the 1600 cm.$^{-1}$ region, and both show the weak but unmistakable C=C band at 1665 cm.$^{-1}$ (Jones, Humphries, Packard, and Dobriner, *J. Amer. Chem. Soc.*, 1950, **72**, 86).

ol and cholest-5-ene-3β : 7α- and -3β : 7β-diol show higher maximal absorption than cholest-4-ene and cholesterol respectively, introduction of a 5α-hydroxyl group into cholest-6-en-3β-ol causes diminished absorption (Bladon, Henbest, and Wood, *J.*, 1952, 2737). The presence of one double bond in the two ethers has been confirmed by titration with permonophthalic acid; Professor Schmid has actually isolated the two crystalline epoxides. A single attempt catalytically to hydrogenate the ether, m. p. 66° (IV), with platinum oxide–acetic acid furnished only cholestane; the catalytic hydrogenation of the epimeric ethers will be further examined in the hope of confirming the structures proposed.

The two ethers are different from cholesteryl methyl ether, m. p. 84°, $[\alpha]_D$ −46°, *epi*-cholesteryl methyl ether, m. p. 89°, $[\alpha]_D$ −46°, 3 : 5-*cyclo*cholestanyl methyl ether, m. p. 79°, $[\alpha]_D$ +55°, and cholest-4-en-3β-yl methyl ether, double m. p. 65° and 81°, $[\alpha]_D$ +23°. The provisional formulæ (IV) and (V) are consistent with the molecular rotations of the isomeric ethers found and calculated (from the constants given by Barton and Klyne, *Chem. and Ind.*, 1948, 755). For the ether, m. p. 66° (IV), $[M]_D$ found −292°; calculated for 4α-methoxycholest-5-ene,* −282°, for 4β-methoxycholest-5-ene, −229°; for the ether, m. p. 96° (V), $[M]_D$ found +328°; calculated for 6β-methoxycholest-4-ene, +346°, for 6α-methoxycholest-4-ene, +249°. The provisional formulæ (IV, V) are also consistent with the conversion of the ethers into cholesta-3 : 5-diene by the action of hydrochloric acid; attack by a proton at a lone pair of the methoxyl-oxygen atom would lead to elimination of methanol and production of cations, which by internal depolarisation would furnish respectively cholesta-3 : 5-diene and cholesta-4 : 6-diene, the latter being known to be converted by hydrochloric acid into the former (Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1941, **63**, 107).

In an attempt to obtain evidence of isomerisation of the cation (II) to cations corresponding to (III) or (V), reduction of *epi*cholesteryl toluene-*p*-sulphonate (I*b*) with lithium aluminium hydride was examined (cf. Karrer and Schmid, *Helv. Chim. Acta*, 1949, **32**, 1371); repeated chromatography of the reduction product led to the isolation only of cholest-5-ene (30%) and cholesta-3 : 5-diene (~40%). The ready formation of the diene appears to be a consequence of the geometry of (I*b*), the facility of the elimination reaction involving four coplanar centres in the transition state (*A*), cutting down the reduction reaction involving simple S_N2 replacement of OTs^- by H^- (cf. Cram, *J. Amer. Chem. Soc.*, 1952, **74**, 2149, 2152).



(*A*)

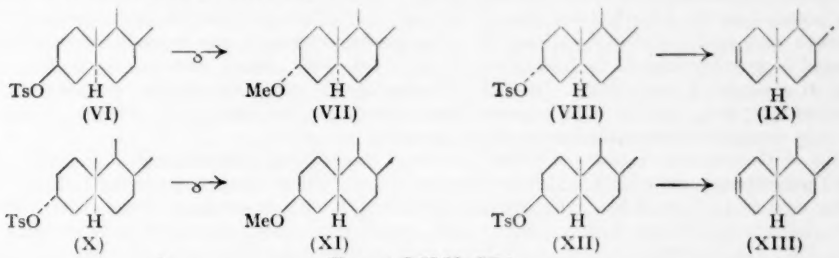
It thus appears that reactions which convert cholesteryl toluene-*p*-sulphonate into derivatives of 3 : 5-*cyclo*cholestane do not permit the conversion of *epi*cholesteryl toluene-*p*-sulphonate into derivatives of 3 : 5-*cyclo*coprostane.

Solvolysis of saturated toluene-*p*-sulphonates occurs with inversion of configuration (Kenyon and Phillips, *J.*, 1923, 44), although in the presence of suitably placed aromatic π-electrons participation can lead to retention of configuration (Winstein, Brown, Schreiber, and Schlesinger, *J. Amer. Chem. Soc.*, 1952, **74**, 1140). The solvolysis of stanyl toluene-*p*-sulphonates was first examined by Stoll (*Z. physiol. Chem.*, 1931, **202**, 232; 1932, **207**, 147; 1937, **246**, 1), and more recently by Plattner (with Fürst and Lang, *Helv. Chim. Acta*, 1943, **26**, 2266; 1944, **27**, 1872), Prelog and Szpilfogel (*ibid.*, 1944, **27**, 390), and Elks and Shoppee (*J.*, 1953, 241). Stoll found that methanolysis of the cholestanyl derivative [VI; 3β-OTs (equatorial)] was largely complete in two hours at 65°, giving a non-crystalline product containing one methoxyl group which we regard as 3α-methoxycholestane (VII) formed with inversion by substitution; when *epi*cholestanyl toluene-*p*-sulphonate [VIII; 3α-OTs (polar)] was refluxed with methanol at 65° 1 : 2-elimination was complete in two hours, yielding cholest-2-ene (IX), m. p. 69°, $[\alpha]_D$ + 64°.

We have examined the reactions of the epimeric coprostanyl toluene-*p*-sulphonates because the stereoelectronic relations here become inverted. *epi*Coprostanyl toluene-*p*-sulphonate [X; 3α-OTs (equatorial)] is unaffected by chromatography on neutralised aluminium oxide; methanolysis is incomplete (82%) after 5 hours at 65° and gives a

* Professor Schmid has informed us recently that he has prepared 4α-methoxycholest-5-ene, m. p. 85—86°, and that it is different from the ether, m. p. 66° (IV), so that this structure must be excluded leaving only the 4β-methoxy-epimeride in the field.

crystalline compound, which we regard as 3β-methoxycoprostane (XI) formed by substitution with inversion, accompanied by only a small amount (18%) of unsaturated hydrocarbon. The coprostanyl derivative [XII ; 3β-OTs (polar)] decomposes readily above 35° and is completely converted by chromatography on neutralised aluminium oxide by a 1 : 2-elimination reaction into coprost-2-ene (XIII), m. p. 47°, $[\alpha]_D$ +23° (some coprost-3-ene may be present in this material).



(Ts = *p*-$C_6H_4Me{\cdot}SO_2$)

The contrasting principal modes of reaction of the A/B-*trans*-epimerides (VI; S_N2; VIII, *E*1 or *E*2) and the A/B-*cis*-epimerides (X, S_N2; XII *E*1 or *E*2) illustrate the influence of molecular geometry and the resulting steric compression on the course of reaction.

Experimental

For general details see *J.*, **1953**, **243**, except that neutralised aluminium oxide * was used for chromatography.

Cholest-5-en-3α-yl Toluene-p-sulphonate.—To *epi*cholesterol (m. p. 140°; 350 mg., dried at 60°/0·01 mm.) in dry pyridine (10 c.c.), purified † toluene-*p*-sulphonyl chloride (900 mg.) was added gradually at 0°. After 3 days at 20°, ice was added and the mixture set aside for 1·5 hr.; the product was extracted with ether, and the extract washed with cold 2N-hydrochloric acid, water, 2N-sodium hydrogen carbonate, and to neutrality with water, dried, and evaporated. The solid residue (484 mg.) was crystallised several times from acetone to give *cholest-5-en-3α-yl toluene-p-sulphonate* (86%), m. p. 96° (with development of a deep red colour; also observed in N_2 or in a vacuum), $[\alpha]_D^{20}$ +6·5° ± 2° (*c*, 1·064 in $CHCl_3$) (Found, after drying at 40—50°/0·005 mm. for 1 hr.: C, 75·4; H, 9·7. $C_{34}H_{52}O_3S$ requires C, 75·5; H, 9·7%).

Cholest-5-en-3α-yl Methanesulphonate.—*epi*Cholesterol (117 mg., dried at 60°/0·01 mm.) in dry pyridine (3 c.c.) was treated dropwise at −10° with methanesulphonyl chloride (0·1 c.c., 4 mols.; prepared according to Johnson and Sprague, *J. Amer. Chem. Soc.*, **1936**, **58**, 1348). The mixture was kept at 20° for 3 days, decomposed with ice, and worked up in the usual way. The colourless solid product (140 mg.) after crystallisation from acetone furnished *cholest-5-en-3α-yl methanesulphonate*, m. p. 110—112° (with production of a red colour), $[\alpha]_D^{20}$ −26° ± 1° (*c*, 0·96 in $CHCl_3$) (Found, after drying at 65°/0·005 mm. for 2 hr.: C, 72·6; H, 10·7. $C_{28}H_{48}O_3S$ requires C, 72·35; H, 10·4%).

Action of Aluminium Oxide.—The above toluene-*p*-sulphonate (50 mg., dried at 20°/0·01 mm. for ½ hr.) was chromatographed on aluminium oxide (1·6 g.) prepared in pentane. Repeated elution with pentane (4 × 5 c.c.) gave fractions (31 mg.), m. p. 74—75°, consisting essentially of cholesta-3 : 5-diene (calc., 33·5 mg.); recrystallisation from acetone–methanol furnished material, m. p. 79° undepressed by admixture with a genuine specimen, and giving an immediate positive Rosenheim test.

Acetolysis.—(a) *With silver acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (100 mg.) and silver acetate (100 mg.) were dried at 50—60°/0·01 mm. for ½ hr., and then refluxed with acetic acid (10 c.c.) under anhydrous conditions for ½ hr., whereafter the bulk of the acetic acid was removed under reduced pressure. The product, isolated in the usual way, formed a pale yellow oil which solidified when dried at 20°/0·01 mm. Crystallisation from ether–ethanol gave colourless needles (26 mg.) of cholesta-3 : 5-diene, m. p. 78°; from the mother-liquor two further crops, m. p. 75—77° (22 mg.) and 73—77° (9 mg.) were obtained. These fractions depressed the m. p.

* Prepared by treatment with 5% nitric acid on a steam-bath for 1 hr., filtration, washing till free from NO_3^-, boiling with methanol, filtration, and reactivation at 250°/10 mm. for 1 hr.

† The ethereal solution was washed with 2N-sodium carbonate, and with water, and evaporated; the product was crystallised several times from benzene, dried in a vacuum, and sealed in small ampoules.

(84°) of *epi*cholesteryl acetate but not that of cholesta-3 : 5-diene, and gave immediate positive Rosenheim tests. The product was unaltered by hot 5% methanolic potassium hydroxide during 2·5 hr., subsequent recrystallisation from ether–ethanol giving fractions, m. p. 78° (9·5 mg.), 76—78° (5 mg.), and 76° (4 mg.), all of which gave immediate positive Rosenheim tests. The residues from these crystallisations were combined with the mother-liquors from the crystallisations of the original acetolysis product and the material (19 mg.) treated with hot 5% methanolic potassium hydroxide; chromatography of the product failed to furnish *epi*cholesterol.

Cholest-5-en-3α-yl methanesulphonate (80 mg.) and silver acetate (75 mg.) were dried and refluxed with acetic acid (5 c.c.) for ½ hr. The product (65 mg.) was crystallised from ether–ethanol to give cholesta-3 : 5-diene (48 mg.), m. p. 76—78°. After removal of a further small crop of crystals (5 mg.), m. p. 70—75°, the residue (11 mg.) obtained by evaporation was chromatographed; elution with pentane gave slightly impure cholesta-3 : 5-diene (6 mg.) as the only crystalline material which could be isolated.

(b) *With potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (100 mg.) and freshly fused potassium acetate (200 mg.) were dried at 40—50°/0·005 mm. for ½ hr. and refluxed with acetic acid (5 c.c.) for 3 hr. The reaction product (71 mg.), crystallised from ether–acetone, gave cholesta-3 : 5-diene (45 mg.), m. p. and mixed m. p. 78°; a second crop (9 mg.) had m. p. 75°. In a repetition, the product was chromatographed on aluminium oxide (2 g.) prepared in pentane. A single elution with pentane gave cholesta-3 : 5-diene (67 mg.), m. p. 76°, giving an immediate positive Rosenheim reaction; hydrolysis with hot 5% methanolic potassium hydroxide and chromatography of the product gave cholesta-3 : 5-diene (61 mg.), m. p. 75°, but no *epi*cholesterol.

Methanolysis.—(a) *In presence of potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (600 mg.) and freshly fused potassium acetate (1·6 g.) were dried together at 20°/0·005 mm. for ½ hr. and refluxed with dry methanol (90 c.c.) under anhydrous conditions for 3 hr. After cooling and addition of water most of the methanol was removed under reduced pressure and the product isolated in the usual way. The crystalline product (436 mg.) was chromatographed on a long column of aluminium oxide (26 g.) prepared in pentane. Elution with pentane (5 × 40 c.c.) gave fractions : A1, m. p. 75° (226 mg.); A2, m. p. 74—91° (43 mg.); A3, m. p. 46—52° (86 mg.); A4, m. p. 61—63° (23 mg.); A5, m. p. 45—53° (2 mg.). Further elution with pentane produced no material, but use of benzene–pentane (1 : 1) and of ether–benzene (1 : 1) gave oils (27 and 5 mg.), which failed to crystallise and were not investigated. Fraction A1 consisted of nearly pure cholesta-3 : 5-diene (mixed m. p.). Fractions A3 and A4 were united and rechromatographed similarly, to give by elution with pentane (7 × 10 c.c.) fractions : B1, oil (7 mg.), discarded; B2, m. p. 58—89° (18 mg.); B3, m. p. 56—60° (32 mg.); B4, m. p. 60·5—63·5° (16 mg.); B5, m. p. 60—63° (7 mg.); B6, m. p. 60—62° (4 mg.); B7, oil (2 mg.). Fractions B3, 4, 5, and 6 were united and recrystallised from ether–methanol, to give 4β-*methoxycholest-5-ene* (IV) (35 mg.), m. p. 66°, $[\alpha]_D^{20}$ −73° ± 2° (*c*, 1·10 in $CHCl_3$) (Found, after drying at 20°/0·005 mm. for 4·5 hr. : C, 83·65; H, 11·85; OMe, 8·1. $C_{27}H_{45}$·OMe requires C, 83·9; H, 12·05; OMe 7·8%), unchanged by sublimation in a high vacuum, giving a pale yellow colour with tetranitromethane in chloroform and a positive Rosenheim test. The yield of the pure compound was 23%, and in a second experiment 19%.

Fractions A2 and B2 were united and rechromatographed, to give by elution with pentane (7 × 6 c.c.) fractions : C1, oil (2 mg.), discarded; C2, m. p. 75—90° (26 mg.); C3, m. p. 89—94° (15 mg.); C4, m. p. 83—89° (7 mg.); C5, 6, and 7, oils (4, 2, and 1·5 mg.), discarded. Fraction C2 was rechromatographed, to give by elution with pentane (4 × 2·5 c.c.) fractions : D1 oil (1·5 mg.), discarded; D2, m. p. 85—93° (15 mg.); D3, m. p. 92—96° (8 mg.); D4, m. p. 88—94° (2·5 mg.). Fraction D2 was again chromatographed to give by elution with pentane (8 × 1·5 c.c.) fractions : E1 no material; E2 and 3, oils (each 1 mg.), discarded; E4, m. p. 89—93° (5 mg.); E5, m. p. 91—94° (3 mg.); E6, m. p. 90—94° (1·5 mg.); E7 and 8 cryst. (1 and 0·3 mg.). Fractions C3, C4, D3, D4, E4—8 were united and recrystallised from methanol, to give 6β-*methoxycholest-4-ene* (V) (17 mg.), needles, m. p. 96°, $[\alpha]_D^{20}$ +82° ± 4° (*c*, 0·523 in $CHCl_3$) (Found, after drying at 55—60°/0·005 mm. for 4·5 hr. : C, 84·2; H, 12·25; OMe, 7·7%), giving a pale yellow colour with tetranitromethane–chloroform and a positive Rosenheim test. The yield of the pure compound was 11% and of cholesta-3 : 5-diene was 57%; in a second experiment 13% and 56% respectively.

(b) *In absence of potassium acetate.* Cholest-5-en-3α-yl toluene-*p*-sulphonate (200 mg., dried at 20°/0·005 mm. for 3 hr.) was refluxed with dry methanol (30 c.c.) with exclusion of moisture for 2·5 hr. Working up as in (a) gave a product (145 mg.). Chromatography on a long column of aluminium oxide (8 g.), prepared in pentane, and elution with pentane (6 × 15

c.c.) gave fractions: F1, m. p. 72—76° (96 mg.); F2, m. p. 55—76° (20 mg.); F3, m. p. 49—57° (7 mg.); F4, m. p. 71—78° (3 mg.); F5, m. p. 68—77° (3 mg.); F6, m. p. 66—77° (1 mg.) Further elution with benzene–pentane and with benzene gave only insignificant traces of oil. Fraction F1 consisted essentially of cholesta-3 : 5-diene, m. p. and mixed m. p. 76°, after recrystallisation from ether–acetone. Fractions F2—6 were united and rechromatographed similarly, to give by elution with pentane fractions: G1, m. p. 59—70° (4 mg.); G2, m. p. 51—69° (26 mg.); G3, oil (3 mg.). Fraction G2 was again chromatographed similarly, to give by elution with pentane fractions: H1, no material; H2, m. p. 85° (6 mg.); H3, oil (13 mg.) which crystallised; H4 and 5, oils (4 and 1 mg.); fraction H2, recrystallised from methanol, gave 6β-methoxycholest-4-ene (V), needles, m. p. 91°, which depressed the m. p. (88—89°) of 3α-methoxycholest-5-ene but not that of the material described under (a). Further chromatography of H3 gave, by elution with pentane, fractions: J1 and 2, no material; J3, m. p. 85—89° (3 mg.); J4, m. p. 84—88° (4 mg.), consisting of 6β-methoxycholest-4-ene (V). The yield of this was 8%; that of cholesta-3 : 5-diene ~75%.

Action of Hydrochloric Acid on the Ethers (IV) *and* (V).—(*a*) 4β-Methoxycholest-5-ene (IV) (12 mg.) was treated in acetic acid (2·5 c.c.) with concentrated hydrochloric acid (0·15 c.c.) at 20° for 19 hr. Crystals were deposi ed and were filtered off (m. p. 70—73°; 8 mg.); recrystallisation from acetone gave cholesta-3 : 5-diene, m. p. and mixed m. p. 77°. Chromatographic examination of the material recovered from the original filtrate furnished no crystals. (*b*) 6β-Methoxycholest-4-ene (V) (10 mg.) similarly gave cholesta-3 : 5-diene.

*Reduction of Cholest-5-en-3α-yl Toluene-*p*-sulphonate with Lithium Aluminium Hydride.*—The compound (600 mg.) was dried at 20°/0·005 mm. for 2·5 hr., dissolved in dry benzene (50 c.c.) and one half of the benzene removed by distillation; the resulting solution was treated with lithium aluminium hydride (500 mg.) in refluxing ether for 22 hr. Excess of reagent was decomposed by dropwise addition of ethyl acetate at 0°, and the product isolated in the usual way as an oil (520 mg.) which crystallised after removal of solvents in a high vacuum (m. p. 46—58°). This material was chromatographed on a long column of aluminium oxide (32 g.) prepared in pentane. Elution with pentane (6 × 50 c.c.) gave fractions: K1, m. p. 59—68° (286 mg.); K2, m. p. 70—74° (40 mg.); K3, oil (3 mg.); K4, 5, 6, no material. Elution with benzene–pentane (1 : 1) gave only traces of oil, but use of benzene gave a yellow oil (23 mg.) from which no crystalline material could be isolated. Fraction K2 consisted essentially of cholesta-3 : 5-diene, m. p. 74·5—76°, after crystallisation from ether–methanol, and had m. p. 75—76° on admixture with a genuine specimen. Fraction K1 was rechromatographed (Al_2O_3; 18 g.) and gave by elution with pentane (5 × 30 c.c.) fractions: L1, m. p. 80—87° (55 mg.); L2, m. p. 60—64° (198 mg.); L3, m. p. 68—74° (20 mg.); L4, m. p. 66—73° (4 mg.); L5, oil (2 mg.), discarded. Fraction L1, recrystallised from acetone–methanol, gave cholest-5-ene, m. p. and mixed m. p. 87—89°, $[\alpha]_D^{20}$ −55°; fractions L3 and L4 consisted essentially of cholesta-3 : 5-diene, m. p. 75—76°, after recrystallisation from ether–methanol. Fraction L2 was rechromatographed (Al_2O_3; 12 g.) and gave by elution with pentane (4 × 15 c.c.) fractions: M1, m. p. 80—86° (40 mg.); M2, m. p. 60—66° (147 mg.); M3, m. p. 66—72° (7 mg.); and M4, oil (1 mg.), discarded. Fraction M1, recrystallised from ether–methanol, gave cholest-5-ene, m. p. 87·5—89·5°. Fractions M2 and M3 were united and again chromatographed (Al_2O_3; 9 g.) and gave by elution with pentane (3 × 10 c.c.) fractions: N1, m. p. 81—85·5° (26 mg.); N2, m. p. 64—69° (109 mg.); N3, m. p. 65—70° (5 mg.). Recrystallisation of N1 from acetone–methanol gave cholest-5-ene, m. p. 86—87°. Fractions N2 and N3 were united and again chromatographed (Al_2O_3; 6 g.), to give by elution with pentane (4 × 5 c.c.); O1, trace; O2, m. p. 69° (75 mg.); O3, m. p. 70° (21 mg.); O4, solid (5 mg.), discarded. Fractions O2 and O3, recrystallised from ether–methanol, gave nearly pure cholesta-3 : 5-diene, m. p. 74° and 74—76°, giving no m. p. depressions on admixture with a genuine specimen and positive Rosenheim tests. The yields of cholest-5-ene and cholesta-3 : 5-diene were thus 30 and ~40% respectively; these two substances were the only crystalline compounds isolated in a second experiment in which the steroid was added to the lithium aluminium hydride.

3α-*Methoxycholest-5-ene.*—Finely divided potassium (65 mg.) and *epi*cholesterol (130 mg.) were shaken in dry benzene (2·5 c.c.) in nitrogen at 25° for 3·5 hr. Methyl iodide (1 c.c.) in benzene (2·5 c.c.) was added and the mixture refluxed for 3·5 hr. The product was a yellow oil (132 mg.) which was chromatographed on aluminium oxide (4 mg.) prepared in pentane. Elution with pentane (5 × 13 c.c.) gave fractions of m. p. 81—86°, 83—88°, 84—88°, 84—87°, 84·5—88°, and 81—86·5° (total, 42 mg.), which were united and crystallised from acetone, to give 3α-methoxycholest-5-ene as plates, double m. p. 80—82° and 88—89°; Wallis and Ford (*J. Amer. Chem. Soc.*, 1937, **59**, 1415) give m. p. 88—89°. Subsequent elution with

benzene and ether–benzene (1 : 19) gave *epi*cholesterol (20 mg.), m. p. 140°, after crystallisation from methanol.

3β-*Methoxycholest*-4-*ene*.—Finely divided potassium (100 mg.) and 3β-hydroxycholest-4-ene (180 mg. prepared according to Plattner *et al.*, *Helv. Chim. Acta*, 1949, **32**, 265) were shaken in dry benzene in nitrogen at 50—60° for 2 hr., whereafter methyl iodide (2·5 c.c.) was added and the mixture refluxed for 3 hr. The product, isolated in the usual way, was chromatographed on aluminium oxide (5 g.) prepared in pentane. Elution with pentane (9 × 20 c.c.) furnished crystalline material in fractions 3—9, m. p. ~60°. These were united (56 mg.) and recrystallised from acetone–methanol, giving 3β-*methoxycholest*-4-*ene*, m. p. 68—70°, $[\alpha]_D^{20}$ −37° ± 2° (*c*, 0·49 in $CHCl_3$) (Found, after drying at 20°/0·01 mm. for 16 hr.: C, 83·85; H, 12·15. $C_{28}H_{48}O$ requires C, 83·9; H, 12·05%).

Coprostan-3α-*yl Toluene*-p-*sulphonate* (prepared by R. J. Bridgwater).—Coprostan-3α-ol (m. p. 116—117°; 600 mg.) in dry pyridine (5 c.c.) and pure toluene-*p*-sulphonyl chloride (430 mg.) were allowed to react at 20° for 60 hr., and furnished an oil (800 mg.) which crystallised on scratching. Recrystallisation from acetone gave the 3α-*toluene*-p-*sulphonate* (520 mg.), m. p. 116—118°, $[\alpha]_D^{18}$ +38° ± 1° (*c*, 1·852 in $CHCl_3$) (Found, after drying at 100°/0·01 mm. for 3 hr.: C, 75·0; H, 10·0. $C_{34}H_{54}O_3S$ requires C, 75·2; H, 10·0%), which depressed the m. p. of coprostan-3α-ol to 95—98°. The compound (50 mg.) was eluted unchanged (m. p. 115—118°; 45 mg.) from aluminium oxide (1·5 g.) by benzene–pentane (1 : 4 and 1 : 2).

Methanolysis. The compound (100 mg.; dried at 50°/0·02 mm. for 1 hr.) was refluxed with dry methanol for 55 hr. Some methanol was removed and a little ether added, whereupon a white solid was deposited and filtered off (m. p. 75—106°; 22 mg.). The product from the filtrate was a yellow oil which was chromatographed on aluminium oxide (2 g.) prepared in pentane. Elution with pentane (4 × 6 c.c.) gave fractions which crystallised when kept and scratched: 1, m. p. 60—61° (9 mg.); 2, m. p. 60—62° (22 mg.); 3, m. p. 60—62° (7 mg.); 4, m. p. 57—60° (2 mg.); but further elution with benzene–pentane (1 : 9, 1 : 4, 1 : 1) and with benzene gave only small amounts of oil. Fractions 1—4 by crystallisation from acetone–methanol yielded 3β-*methoxycoprostane*, double m. p. 64—65° and 79—81°, $[\alpha]_D^{13}$ +23° ± 2° (*c* = 1·038 in $CHCl_3$) (Found, after drying at 30—40°/0·01 mm. for 9 hr.: C, 83·65; H, 12·3; OMe 7·85. $C_{27}H_{47}$·OMe requires C, 83·5; H, 12·5; OMe, 7·7%), giving no colour with tetranitromethane in chloroform. The white solid precipitate gave, by chromatography and elution with pentane, 3β-methoxycoprostane), m. p. 55° and 74° (2 mg.), whilst use of benzene–pentane (1 : 1) furnished coprostan-3α-yl toluene-*p*-sulphonate, m. p. 116—118° (16 mg.). Similar results were obtained in a second experiment. Babcock and Fieser (*J. Amer. Chem. Soc.*, 1952, **74**, 5472) have just described the preparation, by reductive methylation of coprostan-3-one, of a compound, m. p. 62—63°, $[\alpha]_D^{23}$ +27·5°, regarded as 3β-methoxycoprostane.

Coprostan-3β-*yl Toluene*-p-*sulphonate* (prepared by R. J. Bridgwater).—Coprostan-3β-ol (m. p. 100—101°; 600 mg.) gave, as in the preceding esterification, the 3β-*toluene*-p-*sulphonate*, very soluble in acetone but crystallising from acetic acid as plates (346 mg.), m. p. 106—108°, $[\alpha]_D^{18}$ +0·5° ± 1° (*c*, 1·313 in $CHCl_3$) (Found, after drying at 20°/0·01 mm. for 5 hr.: C, 75·1; H, 10·0%), giving no colour with tetranitromethane in chloroform but decomposing readily above 35°. Chromatography on neutralised aluminium oxide, prepared in pentane, and elution with pentane afforded an unsaturated oil, which by crystallisation from ether–methanol furnished *coprost*-2-*ene*, needles, m. p. 46—47°, $[\alpha]_D^{22}$ +23° ± 1° (*c*, 1·59 in $CHCl_3$) (Found, after drying at 35—40°/0·01 mm. for 4 hr.: C, 87·2; H, 12·9. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%). It is not possible to guarantee absence of coprost-3-ene from this material.

epiCholesteryl Chloride.—A considerable series of experiments, with variation of the proportions of the reactants, the order of addition, duration, and temperature, were carried out in which *epi*cholesterol was treated with the following reagents PCl_5–$CaCO_3$–$CHCl_3$, PCl_5–pyridine, PCl_5–$POCl_3$, $SOCl_2$, $SOCl_2$–Et_2O, $SOCl_2$–pyridine, $SOCl_2$–$NPhEt_2$, but failed to give *epi*cholesteryl chloride. Chromatographic examination of the products gave by elution with pentane variable quantities of oil, giving positive Beilstein and Rosenheim tests, which proved extremely difficult to crystallise. Cholesta-3 : 5-diene was sometimes isolated but in poor yield; in the experiments with thionyl chloride a solid, insoluble in ether but crystallisable from benzene (m. p. 238°), was encountered which may have been *epi*cholesteryl sulphite.

Acetolysis. *epi*Cholesteryl chloride (m. p. 107°; 91 mg.; prepared according to Shoppee and Summers, *J.*, 1952, 1790), acetic acid (5 c.c.) and anhydrous potassium acetate (200 mg.) were refluxed for 6 hr.; after dilution with water the product was extracted with pentane, to give in the usual way a colourless oil (86 mg.) which rapidly crystallised. After 1 hour's drying at 60°/0·01 mm., the product (85 mg.) was chromatographed on aluminium oxide (10 g.), and

eluted with pentane (4 × 10 c.c.), to give crystals (83 mg.) which gave the Rosenheim test. Nucleation of a solution in ether–methanol with authentic cholesta-3 : 5-diene caused immediate crystallisation of cholesta-3 : 5-diene (99%) as needles, m. p. 76—78°.

We thank Dr. G. W. Wood for a specimen of pure cholest-3-ene, Dr. S. F. D. Orr of the Chester Beatty Research Institute for measuring the infra-red absorption spectra, and Professor A. Haddow for the permission to use his infra-red spectrometer; we also acknowledge the support of a Grant from The Royal Society (to C. W. S.) and an Award from the Department of Scientific and Industrial Research (to D. D. E.).

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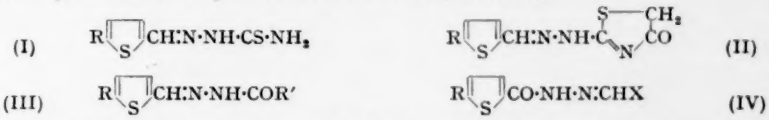
110. *Thiophen Derivatives of Potential Biological Interest. Part IV.* Tuberculostatic Thiophen Compounds.*

By NG. PH. BUU-HOÏ, NG. D. XUONG, RENÉ ROYER, and DENISE LAVIT.

Several 2-thiophenaldehyde thiosemicarbazones bearing a long-chain 5-alkyl substituent, and hydrazides and hydrazones of the thiophen series, have been prepared as potential tuberculostatic compounds.

OWING to the well-known tuberculostatic activity of analogues *in vitro*, thiophen derivatives (I—IV) were prepared in which R was a long-chain alkyl group and R'·CO was nicotinoyl or *iso*nicotinoyl. Standard methods were used.



(I) (II) (III) (IV)

These substances, which are lipoid-soluble, are under biological investigation by Professor Welsch (Liège).

EXPERIMENTAL

Thiophen-aldehydes.—Treatment of *n*-propylthiophen (30 g.), prepared (98% yield) by Kishner–Huang-Minlon reduction of 2-propiothienone, with *N*-methylformanilide (42 g.) and phosphorus oxychloride (42 g.) yielded 5-*n*-propylthiophen-2-aldehyde (29 g.), b. p. 129°/15 mm., n_D^{24} 1·5555 [*thiosemicarbazone*, pale yellow needles (from ethanol), m. p. 119° (Found : C, 47·3; H, 5·5. $C_9H_{13}N_3S_2$ requires C, 47·6; H, 5·7%); 2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol–benzene), m. p. 202° (Found: N, 16·5. $C_{14}H_{14}O_4N_4S$ requires N, 16·8%)]. Kishner–Huang-Minlon reduction of this aldehyde (16 g.) (cf. Buu-Hoï, Hoán, and Xuong, *Rec. Trav. chim.*, 1952, **71**, 285) yielded 2-methyl-5-*n*-propylthiophen (10 g.), b. p. 179°, n_D^{24} 1·5011 (cf. King and Nord, *J. Org. Chem.*, 1949, **14**, 638), which with *N*-methylformanilide (12·5 g.) and phosphorus oxychloride (12·5 g.) yielded 2-*methyl*-5-n-*propylthiophen*-x-*aldehyde* (2 g.), b. p. 130—132°/15 mm., $n_D^{28\cdot5}$ 1·5450 (Found : C, 64·0; H, 7·3. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%) [2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol), m. p. 182° (Found : N, 16·3. $C_{15}H_{16}O_4N_4S$ requires N, 16·1%); a semicarbazone, m. p. *ca.* 228° (decomp.)].

2-*n*-Undecanoylthiophen (Cagniant and Deluzarche, *Compt. rend.*, 1947, **225**, 455), prepared in the usual way (cf. Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, **68**, 5) from thiophen (13·5 g.), *n*-undecanoyl chloride (32 g.), and aluminium chloride (23·5 g.) in carbon disulphide (100 c.c.), was a pale yellow oil (28 g.), b. p. 206°/15 mm., $n_D^{26\cdot5}$ 1·5139, giving a *semicarbazone*, needles (from methanol), m. p. 95—96° (Found : N, 13·4. $C_{16}H_{27}ON_3S$ requires N, 13·6%). By the above reactions it gave 2-n-*undecylthiophen* (15 g. from 25 g.), b. p. 181—183°/18 mm., n_D^{26} 1·4918 (Found : C, 75·4; H, 10·8. $C_{15}H_{26}S$ requires C, 75·6; H, 10·9%), and 5-n-*undecylthiophen*-2-*aldehyde* (9 g. from 14 g.), b. p. 225—226°/18 mm., n_D^{25} 1·5191 (Found : C, 72·0; H, 9·8. $C_{16}H_{26}OS$ requires C, 72·2; H, 9·8%) [*thiosemicarbazone*, pale yellow needles (from ethanol), m. p. 97° (Found : C, 60·0; H, 8·5. $C_{17}H_{29}N_3S_2$ requires C, 60·2; H, 8·6%); 2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol), m. p. 167° (Found : N, 12·3. $C_{22}H_{30}O_4N_4S$ requires N, 12·6%)].

* Part III, *J.*, 1952, 4590.

2-Dodecanoylthiophen (35 g.; cf. Ralston and Christensen, *Ind. Eng. Chem.*, **1937**, **29**, 194), b. p. 212—215°/15 mm., n_D^{25} 1·5060, was similarly prepared and yielded 2-n-*dodecylthiophen* (18 g. from 35 g.), b. p. 184—188°/18 mm., n_D^{25} 1·4783 (Found: C, 76·0; H, 11·3. $C_{16}H_{28}S$ requires C, 76·2; H, 11·1%), and 5-n-*dodecylthiophen-2-aldehyde* (6 g. from 15 g.), b. p. 224—228°/15 mm., pale yellow leaflets (from methanol), m. p. 34° (Found: C, 72·7; H, 10·3. $C_{17}H_{28}OS$ requires C, 72·9; H, 10·0%) [*thiosemicarbazone*, pale yellow needles (from ethanol), m. p. 95° (Found: C, 60·9; H, 9·0. $C_{18}H_{31}N_3S_2$ requires C, 61·2; H, 8·8%); 2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol), m. p. 162° (Found: N, 11·9. $C_{23}H_{32}O_4N_4S$ requires N, 12·2%)].

Similarly were obtained 2-tetradecanoylthiophen (cf. Ralston and Christensen, *loc. cit.*), leaflets (from light petroleum), m. p. 36° [*semicarbazone*, needles (from ethanol), m. p. 108° (Found: N, 11·7. $C_{19}H_{33}ON_3S$ requires N, 12·0%)], 2-n-*tetradecylthiophen* (7 g. from 12 g.), b. p. 212—214°/15 mm., n_D^{23} 1·4845 (Found: C, 76·9; H, 11·3. $C_{18}H_{32}S$ requires C, 77·1; H, 11·4%), and 5-n-*tetradecylthiophen-2-aldehyde* (5·5 g. from 7 g.), b. p. 250—252°/20 mm., leaflets (from ethanol), m. p. 43° (Found: C, 73·7; H, 10·4. $C_{19}H_{32}OS$ requires C, 74·0; H, 10·4%) [*thiosemicarbazone*, needles (from ethanol), m. p. 97° (Found: C, 62·7; H, 9·2. $C_{20}H_{35}N_3S_2$ requires C, 63·0; H, 9·2%); 2 : 4-*dinitrophenylhydrazone*, prisms (from ethanol), m. p. 158° (Found: N, 11·2. $C_{25}H_{36}O_4N_4S$ requires N, 11·5%)].

4-Keto-2-thiazolinylhydrazones of 5-Alkylthiophen-2-aldehydes.—These were prepared by refluxing for 3 hours 1 mol. each of the thiosemicarbazones and chloroacetic acid in ethanol; the precipitates obtained on cooling were recrystallised from acetic acid or ethanol, yielding the *hydrazones* (IV) in which R was n-*propyl*, prisms, m. p. 221° (decomp.) (Found: C, 49·3; H, 4·6. $C_{11}H_{13}ON_3S_2$ requires C, 49·4; H, 4·9%), n-*undecyl*, pale yellow needles, m. p. 163° (Found: C, 60·0; H, 7·8. $C_{19}H_{29}ON_3S_2$ requires C, 60·2; H, 7·7%), n-*dodecyl*, almost colourless needles, m. p. 155° (Found: C, 61·0; H, 7·8. $C_{20}H_{31}ON_3S_2$ requires C, 61·1; H, 7·9%), and n-*tetradecyl*, m. p. 154° (Found: C, 62·6; H, 8·1. $C_{22}H_{35}ON_3S_2$ requires C, 62·7; H, 8·3%).

Hydrazides.—2-Thenoylhydrazine, m. p. 137°, was prepared according to Curtius and Thyssen (*J. pr. Chem.*, **1903**, **65**, 7). 5-*Chloro-2-thenoylhydrazine* (38 g.) was obtained by refluxing ethyl 5-chloro-2-thenoate (40 g.) and 85% hydrazine hydrate (15 g.) in methanol

R	M. p.	Found, % C	Found, % H	Formula	Required, % C	Required, % H
5-R-Thiophen-2-aldehyde N'-nicotinoylhydrazones (III).[a]						
Pr	138°	61·2	5·6	$C_{14}H_{15}ON_3S$	61·5	5·5
$C_{11}H_{23}$	118	68·5	8·2	$C_{22}H_{31}ON_3S$	68·6	8·1
$C_{12}H_{25}$	126	69·1	8·3	$C_{23}H_{33}ON_3S$	69·2	8·3
$C_{14}H_{29}$	129	70·0	8·8	$C_{25}H_{37}ON_3S$	70·3	8·7
5-R-Thiophene-2-aldehyde N'-isonicotinoylhydrazones (III).[a]						
Pr	192	61·4	5·5	$C_{14}H_{15}ON_3S$	61·5	5·5
$C_{11}H_{23}$	128	68·6	8·4	$C_{22}H_{31}ON_3S$	68·6	8·1
$C_{12}H_{25}$	119	69·0	8·4	$C_{23}H_{33}ON_3S$	69·2	8·3
$C_{14}H_{29}$	121	70·1	9·0	$C_{25}H_{37}ON_3S$	70·3	8·7
Thiophen-2-aldehyde N'-5-R-thenoylhydrazones (IV).[a]						
Pr	173	56·0	5·2	$C_{13}H_{14}ON_2S_2$	56·1	5·0
$C_{11}H_{23}$	105	64·3	7·8	$C_{21}H_{30}ON_2S_2$	64·6	7·7
$C_{12}H_{25}$	102	65·2	7·8	$C_{22}H_{32}ON_2S_2$	65·3	7·9
$C_{14}H_{29}$	106	66·4	8·5	$C_{24}H_{36}ON_2S_2$	66·7	8·3
Various N'-2-thenoylhydrazones (IV; R = H).[b]						
Parent X·CHO						
9-Ethylcarbazole-3-aldehyde ...	227°	69·4	4·8	$C_{20}H_{17}ON_3S$	69·2	4·9
Pyrene-3-aldehyde[c]	270	74·3	4·1	$C_{22}H_{14}ON_2S$	74·6	4·0
p-HO·C_6H_4·CHO	>262[f]	58·2	4·0	$C_{12}H_{10}O_2N_2S$	58·5	4·1
4 : 3 : 5 : 1-HO·$C_6H_2Br_2$·CHO ...	>264[f]	35·5	2·3	$C_{12}H_8O_2N_2SBr_2$	35·6	2·0
4 : 3 : 5 : 1-HO·$C_6H_2I_2$·CHO	>237[f]	28·6	2·0	$C_{12}H_8O_2N_2SI_2$	28·9	1·6
p-NMe_2·C_6H_4·CHO	203	61·6	5·5	$C_{14}H_{15}ON_3S$	61·5	5·5
o-C_6H_4Cl·CHO	186	54·2	3·6	$C_{12}H_9ON_2SCl$	54·4	3·4
p-MeO·C_6H_4·CHO	185	60·0	4·8	$C_{13}H_{12}O_2N_2S$	60·0	4·6
3 : 4 : 1-$(MeO)_2C_6H_3$·CHO	171	57·6	4·9	$C_{14}H_{14}O_3N_2S$	57·9	4·8
3 : 4 : 1-$C_6H_3Cl_2$·CHO	219	48·0	2·9	$C_{12}H_8ON_2SCl_2$	48·2	2·7
Ph·CHO[d]	189	54·1	3·5	$C_{12}H_9ON_2SCl$	54·4	3·4
Ph·CHO[e]	201	46·3	3·2	$C_{12}H_9ON_2SBr$	46·6	2·9
3 : 4 : 1-CH_2O_2:C_6H_3·CHO	199	56·8	3·5	$C_{13}H_{10}O_3N_2S$	56·9	3·6
X·CH = 5-Acenaphthylidene[c]	240	70·5	4·6	$C_{18}H_{14}ON_2S$	70·6	4·6

[a] Yellow needles. [b] Colourless unless otherwise stated. [c] Yellow prisms, sparingly sol. in EtOH. [d] 5-Cl in the thenoyl nucleus. [e] 5-Br in the thenoyl nucleus. [f] Decomp.

(30 c.c.) for 12 hours, and crystallised from methanol as leaflets, m. p. 151° decomp. >146° (Found: N, 15·6. $C_5H_5ON_2SCl$ requires N, 15·9%); *ethyl 5-chloro-2-thenoate*, prepared by treating 5-chloro-2-thenoyl chloride with ethanol, had b. p. 234—236° and an aromatic odour (Found: C, 44·0; H, 3·7. $C_7H_7O_2SCl$ requires C, 44·1; H, 3·7%).

5-Bromo-2-thenoylhydrazine, leaflets (from methanol), m. p. 144° (decomp. from 132°) (Found: N, 12·5. $C_5H_5ON_2SBr$ requires N, 12·7%), and ethyl 5-bromo-2-thenoate, b. p. 134—136°/30 mm., were similarly prepared.

Hydrazones.—One mol. each of the hydrazide and aldehyde in ethanol were refluxed for 10 minutes. The precipitates obtained on cooling were recrystallised from ethanol. The *products* are tabulated.

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111. *Urea and Related Compounds. Part II.* The Reaction of Arylureas with Aromatic Sulphinyl and Sulphenyl Chlorides.*

By Frederick Kurzer.

The main products of the interaction of arylureas and aromatic sulphinyl chlorides in pyridine are *N*-aryl-*N'*-arylsulphinyl- and *N*-aryl-*N'*-arylsulphenyl-ureas. The latter products are also formed from arylureas and sulphenyl chlorides. The structures of both classes of compounds are established by their oxidative conversion into *N*-aryl-*N'*-arylsulphonylureas. Some properties of sulphinyl- and sulphenyl-ureas, particularly their hydrolysis under various conditions, are described.

The results obtained in the reactions of aromatic ureas and thioureas with sulphonic and carboxylic acid chlorides suggested that the related reaction between ureas and sulphinyl chlorides might yield either sulphinylcyanamides, R'·SO·NR·CN, or sulphinylureas (I) (Kurzer, *Chem. Reviews*, 1952, **50**, 1, 13). The synthesis of compounds of this type had apparently not been previously described: the only relevant publication (Geigy, Swiss P. 261,774) refers to a conversion of one sulphinylurea, of undisclosed origin, into another.

Benzene- and toluene-*p*-sulphinyl chlorides (2—2·5 mols.) were found to react with arylureas (1 mol.) in pyridine at moderate temperatures to yield *N*-aryl-*N'*-arylsulphinylureas (25—30%) and *N*-aryl-*N'*-arylsulphenylureas (25—30%) as main products. The appropriate arylsulphonic acid (in amounts approximately equivalent to that of the sulphenylurea), and the aryl arylthiolsulphonate, arising from the excess of the acid halide, were also isolated. The ease, with which disproportionations occur in reactions involving sulphinic acids and their derivatives necessitated very careful control of the experimental conditions in the sulphinyl chloride–urea reaction: the use of slightly higher temperatures, or insufficient amounts of solvent, or the presence of moisture or traces of thionyl chloride caused serious or complete destruction of the reactants. Details concerning this general reaction are summarised in the Table (p. 553).

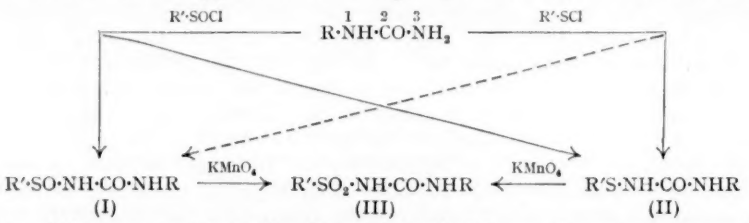
The reaction presents two chief features of interest: first, sulphinyl halides, in their interaction with arylureas, resemble halides of carboxylic acids rather than those of sulphonic acids. Unlike sulphonyl halides, which initially attack at the oxygen atom of the enolic urea configuration, forming unstable intermediate *O*-sulphonylureas, R·NH·C(:NH)·O·SO_2R', and yielding cyanamides by the immediate elimination of sulphonic acids, R'·SO_3H, sulphinyl halides cause substitution at $N_{(3)}$ directly.

The second point of special interest is the unexpected formation of sulphenyl derivatives. Since the corresponding sulphinylcyanamides would have similar properties, and almost the same ultimate composition (corresponding derivatives differing only by two atoms of hydrogen), the structure of the sulphenylureas (II) was confirmed by their synthesis from the urea and sulphenyl chloride, and by their oxidation to *N*-aryl-*N'*-arylsulphonylureas (see below). The sulphinyl halides, prepared as usual, afforded only sulphinamides with

* The communication, *J.*, 1949, 2292, is regarded as Part I of this series. The present results have been reported in a preliminary summary (*Nature*, 1952, **170**, 167).

amines and were therefore substantially free from sulphenyl chlorides. It is unlikely that the reaction under discussion is preceded by the change of sulphinyl halides into sulphenyl and sulphonyl halides (or their equivalents in pyridine solution), since the latter would convert part of the urea into an *N*-aryl-*N*-arylsulphonylcyanamide (*J.*, 1949, 3029). Finally, sulphinylureas were found to be stable under the prevailing experimental conditions and, once formed, cannot be expected to give rise to sulphenylureas. It is therefore suggested that the simultaneous formation of sulphinyl- and sulphenyl-ureas occurs by a rapid disproportionation, during which a proportion of the sulphinyl residues is converted into equal amounts of sulphenyl and sulphonyl units, a conclusion which is supported by the isolation of an equivalent of sulphonic acid. The precise stage at which the postulated disproportionation occurs cannot be specified, but may well involve arylsulphinyl cations, $R{\cdot}SO^+$, and their reactivity probably explains the necessity for careful control of the experimental conditions in the urea–sulphinyl chloride reaction. It seems significant that comparable reactions of sulphinyl chlorides with numerous other compounds are not complicated by the parallel production of sulphenyl derivatives (*e.g.*, amines: von Braun and Kaiser, *Ber.*, 1923, **56**, 549; Raiford and Hazlet, *J. Amer. Chem. Soc.*, 1935, **57**, 2172; esters: Phillips, *J.*, 1925, **127**, 2552). Although oxidation–reduction phenomena in syntheses involving arylsulphinic acids are common, the present example appears to be first in which the use of sulphinyl halides introduces sulphenyl radicals into organic structures.

In view of the above results the corresponding reaction involving sulphenyl halides was examined. A sulphenylurea has recently been obtained from 4-nitrobenzenesulphenyl chloride and benzylurea in benzene (Geigy, *loc. cit.*). Under the usual experimental conditions, sulphenyl chlorides and arylureas were found to afford good yields of *N*-aryl-*N'*-arylsulphenylureas (II). Varying quantities of diaryl disulphides, arising from the excess of sulphenyl chlorides employed, appeared as by-products, and small amounts of the corresponding sulphinylureas (I) were also isolated in some experiments. Owing to the absence of the mobile oxygen atom in sulphenyl chlorides, an oxidation–reduction



mechanism of the type postulated for the sulphinyl halide reaction cannot account for the formation of sulphinylureas in the present conversion. Since sulphinylureas were never formed in yields exceeding 3%, atmospheric oxidation is probably responsible for their production in these instances. The sulphenyl chloride–urea synthesis proved to be much less sensitive than the corresponding reaction of sulphinyl halides. This observation is explained by the absence of disproportionations in the former case. Various sulphenylureas synthesised by this procedure were identical with samples prepared by the sulphinyl halide method (cf. Tables, p. 553).

In contrast to sulphonylureas of analogous structure (*J.*, 1951, 1258), sulphinylureas are generally easily crystallisable, sparingly soluble solids. Owing to the presence of the –NH·SO– grouping, they behave as weak acids and dissolve in alkalis with formation of salts. Aqueous solutions of their sodium or potassium salts are strongly alkaline; the salts are precipitated from their concentrated solutions by addition of an excess of sodium or potassium hydroxide. Fairly consistent results for the molecular weights of sulphinylureas are obtainable by titration with alkali in aqueous acetone, phenolphthalein being used as indicator. Sulphenylureas, on the other hand, are insoluble in alkali hydroxides. This result agrees with the observation that structurally similar sulphenamides display no acid properties: *o*-nitrobenzenesulphenamides, for example, are insoluble in 10% sodium hydroxide solution (Billman and O'Mahony, *J. Amer. Chem. Soc.*, 1939, **61**, 2340).

On storage at room temperature, *N*-aryl-*N'*-arylsulphinylureas decomposed slowly

(during 2—8 weeks) into viscous oils, which consisted of arylureas, aryl arylthiolsulphonates, and sulphonic acids. In a dry atmosphere at 0°, however, pure specimens of sulphinylureas remained unchanged indefinitely. The decomposition is probably initiated by slow hydrolysis into arylurea and sulphinic acid (eqn. 1), the latter disproportionating subsequently in the familiar manner (eqn. 2). Since the yields of arylsulphonic acids predominated over those of the aryl arylthiolsulphonates, some direct oxidation of the intermediate sulphinic to sulphonic acids must also occur (eqn. 3) (cf. Experimental section, p. 554). Sulphenylureas, on the other hand, proved to be stable at room temperature. Like the sulphinyl analogues, they decompose at the m. p.

Hydrolysis of sulphinyl- and sulphenyl-ureas under various conditions gave results in agreement with the suggested formulæ. Alkaline hydrolysis of *N*-phenyl-*N'*-toluene-*p*-sulphinylurea gave aniline, ammonia, and toluene-*p*-sulphinic acid, the latter being identified as the benzylthiuronium salt (*J.*, 1952, 3728). Phenylurea was obtained in acid, the sulphinic acid being directly converted into sulphonic acid and thiosulphonate ester (eqn. 2).

$$R'\cdot SO\cdot NH\cdot CO\cdot NHR + H_2O \longrightarrow R'\cdot SO_2H + R\cdot NH\cdot CO\cdot NH_2 \quad (1)$$

$$3R'\cdot SO_2H \xrightarrow{70\%} R'\cdot SO_2\cdot S\cdot R' + R'\cdot SO_3H + H_2O \quad (2)$$

$$3R'\cdot SO_2H \xrightarrow{30\%} 3R'\cdot SO_3H \quad (3)$$

Alkaline fission of sulphenylureas (II) gave, in addition to the appropriate urea, an aromatic thiol and a sulphinic acid. With one exception, sulphenic acids are not known in the free state, but rearrange, according to conditions, into a variety of products (Kharasch Potempa, and Wehrmeister, *Chem. Reviews*, 1946, **39**, 269). In the presence of alkali, the disproportionation terminates with the formation of the sodium salts of thiols and sulphinic acids. The production of the above compounds thus supports the view that hypothetical sulphenic acids occur as intermediates in this hydrolysis. In the acid fission, the arylsulphenyl residue was isolated as diaryl disulphide and arylthiolsulphonate; these may again be visualised as arising from the primary sulphenic acids (eqns. 4—6), resulting in the overall reaction (7):

$$2R'\cdot S\cdot OH \longrightarrow R'\cdot SH + R'\cdot SO_2H \quad (4)$$

$$R'\cdot SH + R'\cdot S\cdot OH \longrightarrow R'S\cdot SR' + H_2O \quad (5)$$

$$R'\cdot SO_2H + R'\cdot S\cdot OH \longrightarrow R'\cdot SO_2\cdot SR' + H_2O \quad (6)$$

$$4R'\cdot S\cdot OH \longrightarrow R'S\cdot SR' + R'\cdot SO_2\cdot SR' + 2H_2O \quad (7)$$

With acetic anhydride, containing small quantities of concentrated sulphuric acid, sulphenylureas (II) gave *N*-acetyl-*N'*-arylureas and diaryl disulphides; the formation of the latter from the hypothetical sulphenic acid may again be explained by a disproportionation such as (8). The observed yields of disulphide are in agreement with this view.

$$5R'\cdot S\cdot OH \longrightarrow 2R'S\cdot SR' + R'\cdot SO_3H + 2H_2O \quad (8)$$

The structures of the sulphinyl- (I) and sulphenyl-ureas (II) were confirmed, and the position of the substituents in the molecule demonstrated by oxidation of both series by alkaline potassium permanganate to known *N*-aryl-*N'*-arylsulphonylureas (III). Reaction was rapid at room temperature when the reagent was added to a solution of the sulphinylurea in dilute alkali; the alkali-insoluble sulphenylureas were successfully oxidised, though in lower yields, in suspension. Absence of rearrangements under the very mild conditions of the oxidation may reasonably be assumed. Further structural proof, obtained by an unequivocal synthesis of sulphenylureas from sulphenamides, will be detailed later.

The sulphinyl chlorides were prepared by action of a large excess of thionyl chloride on the stable hydrated sodium sulphinates rather than on the free acids. This variation of the standard method (Hilditch and Smiles, *Ber.*, 1908, **41**, 4115) avoids the preliminary isolation and troublesome drying of the labile arylsulphinic acids and gives excellent yields of benzene- and toluene-*p*-sulphinyl chlorides. The possible destructive action of the excess of thionyl chloride on the freshly formed sulphinyl chloride (Hilditch, *J.*, 1910, **97**, 2579) was not encountered at the lower temperatures used. The present results differ from the report by Knoevenagel and Römer (*Ber.*, 1923, **56**, 217) that only benzenesulphonyl chloride and

phenyl benzenethiolsulphonate are formed from sodium benzenesulphinate and thionyl chloride in ether.

Experimental

Analyses are by Drs. Weiler and Strauss, Oxford.

Toluene-p-*sulphinyl Chloride*.—To thionyl chloride (74·4 g., 0·625 mole), finely powdered sodium toluene-*p*-sulphinate dihydrate (26·75 g., 0·125 mole) was added in portions during 10 minutes. Reaction occurred with vigorous evolution of hydrogen chloride and sulphur dioxide, but after a slight spontaneous warming on the addition of the first portion of sulphinate the temperature of the reaction mixture fell to 0—5° during the addition of the remainder. The ice-cold mixture was set aside for 1½ hours, during which the suspended white granular material gradually changed into translucent crystals. The excess of thionyl chloride was then distilled off below 45° in a vacuum, and the last traces were removed by twice adding ether (40 ml.; dried over P_2O_5) and repeating the evaporation. The crude toluene-*p*-sulphinyl chloride was readily separated from the suspended sodium chloride by dissolution in ether (80 and 20 ml.) and rapid decantation; removal of the solvent left almost pure sulphinyl chloride as a pale yellow viscous oil (86—92%). Vacuum-distillation gave the product as a deep yellow, mobile oil, b. p. 113—115°/3·5 mm., 99—102°/0·5 mm. (14·4—16·2 g., 66—74%).

Interaction of Phenylurea and Toluene-p-*sulphinyl Chloride*.—The freshly prepared sulphinyl chloride (not purified by vacuum-distillation, quantities as above) was added, in one portion, at room temperature, to a solution of phenylurea (6·8 g., 0·05 mole) in anhydrous pyridine (80 ml.). The resulting deep orange liquid, the temperature of which rose to 45—48°, was set aside for 4—5 minutes, and was then slowly stirred into a mixture of water (300 ml.), ice (300 g.), and concentrated hydrochloric acid (100 ml.). The separated oil soon solidified and was then filtered off (filtrate B), washed by successive grinding in a mortar with dilute hydrochloric acid and water, and drained (dry weight, 12—15 g.). The material was stirred for half-hour periods with successive portions of sodium hydroxide solution (6% w/v, 80 ml. at 30°; 3% w/v, 60 ml. at 45°; 60 ml. at 65°) (insoluble residue A). The combined filtrates were filtered (charcoal) and gave, on slow acidification with concentrated hydrochloric acid (Congo-red) at 0°, a copious white precipitate (4·5 g., 33%). Two crystallisations, by dissolution in boiling ethanol and dilution with water (30 ml. and 10 ml. respectively, per g.), gave platelets of N-*phenyl*-N′-*toluene*-p-*sulphinylurea*, m. p. 164—167° (decomp.) (2·5 g.) [Found: C, 61·35; H, 5·4; N, 9·9; S, 11·5%; *M* (Rast), 258, 265; *M* (titration in acetone with 0·2N-sodium hydroxide; phenolphthalein), 280. $C_{14}H_{14}O_2N_2S$ requires C, 61·3; H, 5·1; N, 10·2; S, 11·7%; *M*, 274]. The mother-liquors gave a second crop of satisfactory purity on rapid evaporation in a vacuum to quarter-bulk at the lowest possible temperature (Total yield: 3·5—4·0 g., 25—30%). The product was soluble in hot acetone, ethanol, and benzene, and in dilute alkalis with formation of salts, and was unchanged by pyridine during 15 minutes at 60°.

The alkali-insoluble residue A (4·5—5·0 g.) was twice heated with water (70 ml.) to 100° to remove any sulphinylurea and traces of unchanged phenylurea. Crystallisation once from aqueous ethanol [ethanol (10 ml.), water (4 ml.) per g.] and twice from ethanol (25 ml. per g.) gave N-*phenyl*-N′-*toluene*-p-*sulphenylurea*, needles, m. p. 171—173° (decomp.) (yield, including material from mother-liquors, 3·2 g., 25%) [Found: C, 65·2; H, 5·8; N, 10·8; S, 12·2%; *M* (Rast), 244, 258. $C_{14}H_{14}ON_2S$ requires C, 65·1; H, 5·4; N, 10·85; S, 12·4%; *M*, 258]. The final mother-liquors contained *p*-tolyl toluene-*p*-thiolsulphonate (0·5—1·1 g.; m. p. 77°).

The aqueous filtrate B was evaporated slowly on the steam-bath to small volume (120 ml.) during 6—8 hours. The small oily deposit (0·2—0·5 g., obtained in some experiments only) was *p*-tolyl toluene-*p*-thiolsulphonate (m. p. 76—77°; from ethanol). The pale yellow syrup was adjusted to pH 8 with alkali, diluted with water (to 250 ml.), and treated with a saturated aqueous solution (60°) of *S*-benzyl*iso*thiourea hydrochloride (8 g.). Platelets of benzylthiuronium toluene-*p*-sulphonate (3·6 g., 86% calc. on the amount of sulphenylurea formed), m. p. 182—183° (from aqueous ethanol), were obtained on storage at 0°.

The Table summarises the use of this general method for the preparation of analogous *compounds*.

Spontaneous Decomposition of N-Aryl-N′-arylsulphinylureas.—Pure *N*-phenyl-*N*′-toluene-*p*-sulphinylurea (1·37 g., 0·005 mole) retained its crystalline form for 4—8 weeks at room temperature in closed vessels, but then had m. p. 100—120° and had become highly soluble in ethanol; on further short storage, conversion into an orange highly viscous oil occurred. Extraction with boiling water (2 × 10 ml.) (extracts A) and crystallisation of the residue from ethanol (8 ml.) (carbon) gave *p*-tolyl toluene-*p*-thiolsulphonate, prisms (0·31 g., 68%), m. p. 77—78° (Found:

N-*Aryl*-N′-*arylsulphinylureas*, R·SO·NH·CO·NHAr.[a]

No.	R	Ar	Temp. of prep.[b]	Yield, %[c]	M. p. (decomp.)[d]	Cryst. solvent
1	Ph	Ph	18—45°	35	162—164°	EtOH
2	Ph	*p*-C_6H_4Me	18—45	24	190—191	Aq. EtOH
3	*p*-C_6H_4Me	*p*-C_6H_4Me	18—42	42	161—163	,,
4	*p*-C_6H_4Me	*p*-C_6H_4Ph	18—50	12	206—207	EtOH
5	*p*-C_6H_4Me	α-$C_{10}H_7$	18—35	36	190—192	$COMe_2$–EtOH
6	*p*-C_6H_4Me	*p*-EtO·C_6H_4	18—50	30	189—191	Aq. EtOH
			5—44	2	191—192	EtOH
7	*p*-C_6H_4Me	*p*-C_6H_4Cl	18—40	36	166—168	Aq. EtOH

N-*Aryl*-N′-*arylsulphenylureas*, RS·NH·CO·NHAr.[a]

8	Ph	Ph	18—45°	32	180—182°	EtOH
9	Ph	*p*-C_6H_4Me	18—45	36	196—197	,,
10	*p*-C_6H_4Me	*p*-C_6H_4Me	18—42	30	192—193	,,
11	*p*-C_6H_4Me	*p*-C_6H_4Ph	20—40	20	204—205	Aq. EtOH
12	*p*-C_6H_4Me	α-$C_{10}H_7$	18—35	34	214—215	EtOH or $COMe_2$–EtOH
13	*p*-C_6H_4Me	*p*-MeO·C_6H_4	12—40	33	201—202	EtOH
14	*p*-C_6H_4Me	*p*-EtO·C_6H_4	5—40	42	202—204	,,
			5—44	68	202—203	,,
15	*p*-C_6H_4Me	*p*-C_6H_4Cl	5—35	40	177—178	$COMe_2$–EtOH
16	*p*-C_6H_4Me	*p*-C_6H_4Br	18—45	42	199—200	EtOH

N-*Aryl*-N′-*arylsulphinylureas*, R·SO·NH·CO·NHAr.[a]

		Found, %				Required, %			
No.	Formula	C	H	N	S	C	H	N	S
1	$C_{13}H_{12}O_2N_2S$	60·0	4·6	10·5	11·95	60·0	4·6	10·8	12·3
2	$C_{14}H_{14}O_2N_2S$	61·0	5·3	9·95	11·8	61·3	5·1	10·2	11·7
3	$C_{15}H_{16}O_2N_2S$[f]	62·4	5·2	9·7	11·1	62·5	5·6	9·7	11·1
4	$C_{20}H_{18}O_2N_2S$	69·1	5·4	8·5	8·8	68·6	5·1	8·0	9·1
5	$C_{18}H_{16}O_2N_2S$	67·0	4·9	—	—	66·7	4·9	—	—
6	$C_{16}H_{18}O_3N_2S$[g]	60·35	5·8	—	—	60·4	5·7	—	—
	,,	60·2	5·6	—	—	—	—	—	—
7	$C_{14}H_{13}O_2N_2SCl$	54·7	4·1	8·7	10·3	54·5	4·2	9·0	10·4

N-*Aryl*-N′-*arylsulphenylureas*, R·S·NH·CO·NHAr.[a]

8	$C_{13}H_{12}ON_2S$	63·6	5·0	11·1	12·7	63·9	4·9	11·5	13·1
9	$C_{14}H_{14}ON_2S$	65·0	5·3	—	—	65·1	5·4	—	—
10	$C_{15}H_{16}ON_2S$[h]	65·7	5·6	10·3	11·9	66·2	5·9	10·3	11·8
11	$C_{20}H_{18}ON_2S$	71·8	5·4	9·0	9·7	71·8	5·4	8·4	9·6
12	$C_{18}H_{16}ON_2S$	69·7	5·3	—	—	70·1	5·2	—	—
13	$C_{15}H_{16}O_2N_2S$	62·8	5·4	—	—	62·5	5·55	—	—
14	$C_{16}H_{18}O_2N_2S$[i]	63·3	6·05	9·8	10·9	63·6	6·0	9·3	10·6
	,,	63·7	6·2	—	—	—	—	—	—
15	$C_{14}H_{13}ON_2SCl$[j]	57·5	4·4	9·3	—	57·4	4·4	9·6	—
16	$C_{14}H_{13}ON_2SBr$[k]	50·0	3·8	—	—	49·9	3·9	—	—

[a] Obtained from arylureas and sulphinyl chlorides, except for nos. 13 and 16 which were prepared by means of the sulphenyl chlorides. Nos. 6 and 14 were obtained by both methods. [b] *Sulphinyl chlorides.* When the stated reaction time and temperature were exceeded (*e.g.*, 20 min.; 56—60°), the addition of the resulting deep orange liquid to ice-water gave orange oils which failed to solidify on prolonged storage at 0°. The expected products were still obtained but in low yield, with a greater proportion of *p*-tolyl toluene-*p*-thiolsulphonate, by dissolving the oil in benzene, extracting the sulphinylurea with alkali, and isolating the sulphenylurea from the washed neutral benzene layer. Temperatures of 60—80° (owing to incomplete removal of thionyl chloride, use of an insufficient volume of solvent, or too high an initial temperature) gave intractable oils of pungent odour. *Sulphenyl chloride.* The spontaneous temperature rise was less pronounced, and failure of experiments due to this cause was not observed. In some instances, the reaction mixture had to be warmed to the required temperature. [c] Average of 2—3 expts. [d] Variable, depending on the rate of heating, width of m. p. tube, etc. Therefore the specimen was inserted into the apparatus about 30—40° below the approx. m. p., and the temp. raised at approx. 20°/min. M. p.s of sulphenylureas were reproduced without difficulty. On fusion, sulphinylureas generally gave a deep violet to black mass, while sulphenylureas decomposed to a deep orange-red melt. [e] Sulphinylureas, platelets; sulphenylureas, generally needles. Both series were, as a rule, first crystallised by diluting their boiling saturated ethanolic solution with 0·25—0·33 vol. of water, which resulted in a satisfactory recovery of nearly pure products. All the compounds were fairly sparingly soluble, requiring generally 60—100 ml. (but some members up to 200 ml.) of boiling ethanol per g. The substances were finally purified from the solvents stated. [f] Found: *M* (titration), 294. Required: 288. [g] Found: *M* (titration), 310. Required: 318. [h] Found: *M* (Rast), 245. Required: 272. [i] Found: *M* (Rast), 280. Required: 302. [j] Found: Cl, 12·35. Required: 12·1%. [k] Found: Br, 23·5. Required: 23·7%.

C, 60·4; H, 4·9. Calc. for $C_{14}H_{14}O_2S_2$: C, 60·4; H, 5·0%). The extracts A, on cooling and partial spontaneous evaporation, deposited phenylurea (0·49 g., 72%), m. p. and mixed m. p. 148° (from aqueous ethanol). The aqueous filtrates, treated with hot saturated aqueous *S*-benzyl*iso*thiourea hydrochloride (2·0 g.) and cooled to 0°, deposited benzylthiuronium toluene-*p*-sulphonate, m. p. 182—183° (from aqueous ethanol) (0·90 g.; 0·40 g. thereof corresponds to the 68% yield of *p*-tolyl toluene-*p*-thiolsulphonate, formed according to eqn. 2; the rest is formed by direct oxidation of the primarily produced sulphinic to sulphonic acid, to the extent of 29%).

When stored in open vessels, sulphinylureas decomposed more rapidly (1—2 weeks), as did specimens that had only been purified by reprecipitation from alkaline solution. In a dry atmosphere at 0°, crystalline sulphinylureas remained unchanged for at least 12—18 months, though their m. p.s had sometimes dropped by several degrees.

Alkaline Hydrolysis of N-*Phenyl*-N′-*toluene*-p-*sulphinylurea*.—The sulphinylurea (1·65 g., 0·006 mole) in aqueous sodium hydroxide (6% w/w; 60 ml.) was boiled under reflux for 2 hours. Ammonia was evolved and drops of oil appeared. The solution was then subjected to slow downward distillation, the volume of the residual liquid being kept constant by the simultaneous dropwise addition of water (residual liquid A). The distillate, the first few ml. of which contained oil, was made strongly alkaline and exhaustively extracted with ether, and the isolated aniline collected as the acetyl derivative (m. p. 113—114°; 0·72 g., 89%).

The residual liquid (A) contained toluene-*p*-sulphinic acid (iron and copper salt tests). It was strongly acidified with concentrated hydrochloric acid (15 ml.) and slowly evaporated twice on the steam-bath nearly to dryness during 4 hours, and the residue was stirred with water (30 ml.). The separated oil solidified and, crystallised from aqueous ethanol, gave *p*-tolyl toluene-*p*-thiolsulphonate, m. p. and mixed m. p. 76° (0·48 g., 86%). The aqueous filtrate from the solidified oil gave benzylthiuronium toluene-*p*-sulphonate, m. p. 181—182° (0·59 g., 88%). Alternatively, toluene-*p*-sulphinic acid was directly obtained as the benzylthiuronium salt, m. p. and mixed m. p. 167—168°, in 82% yield (Kurzer and Powell, *J.*, 1952, 3728). A control experiment showed that sodium toluene-*p*-sulphinate is not decomposed during 2 hours' boiling with 6% aqueous sodium hydroxide.

Acid Hydrolysis of N-*Phenyl*-N′-*toluene*-p-*sulphinylurea*.—The sulphinylurea (1·37 g., 0·005 mole) in absolute ethanol (50 ml.)–hydrochloric acid (12 ml.) was refluxed for 2 hours, most of the solvent removed in a vacuum, and the residual liquid diluted with water (20 ml.). The solidified oil was filtered off (filtrate A) and extracted with boiling water (10 ml.) (extracts B). The residue was crystallised from ethanol, giving *p*-tolyl toluene-*p*-thiolsulphonate, m. p. 76—77° (0·29 g., 62%). On cooling and partial evaporation, the extracts B deposited phenylurea, m. p. 147° (0·20 g., 30%). The filtrate A contained aniline hydrochloride, which was isolated by partial evaporation and identified as acetanilide (0·39 g., 58%; *i.e.*, total recovery of the *N*-aryl part of the molecule, 88%).

Interaction of Phenylurea and Toluene-p-*sulphenyl Chloride*.—Phenylurea (6·8 g., 0·05 mole) in pyridine (100 ml.) at 10° was rapidly treated with toluene-*p*-sulphenyl chloride (15·85 g., 0·1 mole) (Lecher *et al.*, *Ber.*, 1924, **57**, 755; 1925, **58**, 409). The red colour of the chloride was momentarily discharged but reappeared as the temperature of the liquid rose to 40—45°. After 5 minutes, the solution was slowly stirred into water (250 ml.)–ice (250 g.)–concentrated hydrochloric acid (100 ml.), and after several hours the aqueous phase was decanted from the coagulated orange viscous resin-like material. The latter was vigorously stirred with aqueous sodium hydroxide (100 ml., 5% w/v) for 15 minutes. The soft resin changed into friable pale-yellow fragments which were filtered off (alkaline extracts A) and several crystallisations from ethanol gave *N*-phenyl-*N*′-toluene-*p*-sulphenylurea (6·45—7·1 g.; 50—55%), m. p. and mixed m. p. 171—173° (decomp.) (Found: C, 64·8; H, 5·0. Calc. for $C_{14}H_{14}ON_2S$: C, 65·1; H, 5·4%). The final mother-liquors deposited, on slow evaporation, varying quantities (2—3 g.) of di-*p*-tolyl disulphide, m. p. 46—47° (from ethanol).

The extracts A gave a white solid [m. p. 180° (decomp.); 0·42 g.] on acidification; crystallisation from ethanol yielded *N*-phenyl-*N*′-toluene-*p*-sulphinylurea, m. p. 165—166° (decomp.) (Found: C, 61·7; H, 5·3. Calc. for $C_{14}H_{14}O_2N_2S$: C, 61·3; H, 5·1%).

The Table records the similar preparation of four *analogues*.

Alkaline Hydrolysis of N-p-*Ethoxyphenyl*-N′-*toluene*-p-*sulphenylurea*.—To a solution of the sulphenylurea (3·02 g., 0·01 mole) in ethanol (75 ml.), potassium hydroxide (4·5 g.) in water (6 ml.) was added. The clear liquid obtained after 20 minutes' refluxing was partially neutralised by concentrated hydrochloric acid (5 ml.), most of the ethanol removed in a vacuum, and the residue treated with water (50 ml.). The resulting suspension was cooled to 0° and the separated

p-ethoxyphenylurea (1·55 g., 86%; m. p. 174—175° from ethanol) filtered off. The filtrate was made strongly acid and steam-distilled. The oil which separated from the distillate (100 ml.) and solidified consisted of thio-*p*-cresol (0·29 g., 47%; m. p. 43—44°; benzoyl derivative, m. p. 75—76°). The acid residual liquid from the thio-*p*-cresol on slow evaporation gave *p*-tolyl toluene-*p*-thiolsulphonate (0·32 g., 70%), m. p. 77° (from ethanol).

Acid Hydrolysis of N-*Toluene*-p-*sulphenyl*-N′-p-*tolylurea*.—The sulphenylurea (2·72 g., 0·01 mole), suspended in absolute ethanol (60 ml.), dissolved instantly on addition of hydrochloric acid (15 ml.). The clear liquid was refluxed for 2 hours, the solvent removed nearly completely in a vacuum, and the residue stirred with cold water (30 ml.). The separated solidified oil (2·8 g.) was filtered off (filtrate A), and extracted with boiling water (3 × 15 ml.) (aqueous extracts B). The water-insoluble residual dark oil was dissolved in ethanol (20 ml.), and the solution filtered (charcoal), and allowed to evaporate spontaneously; white feathery crystals and massive prisms separated. Mechanical separation and recrystallisation gave di-*p*-tolyl disulphide, m. p. 45—46° (0·42 g., 68%), and *p*-tolyl toluene-*p*-thiolsulphonate, m. p. 76° (0·35 g., 50%) (both yields calc. according to eqn. 7). The extracts B gave, on partial evaporation *in vacuo* and recrystallisation from boiling water, *p*-tolylurea, m. p. 180—181° (0·80 g., 53%) (Found: N, 18·7. Calc. for $C_8H_{10}ON_2$: N, 18·7%). The filtrate A contained the hydrochloride of *p*-toluidine, which was isolated from the basified solution with ether and identified as the acetyl derivative, m. p. 148° (0·12 g.).

Hydrolysis of Sulphenylureas by Acetic Anhydride–Sulphuric Acid.—(*a*) *N*-*p*-Chlorophenyl-*N*′-toluene-*p*-sulphenylurea (0·87 g., 0·003 mole) was added to acetic anhydride (8 ml.) and concentrated sulphuric acid (1 drop), and the resulting solution boiled for 3 minutes. Its initial deep violet colour faded rapidly; the orange-red liquid obtained was kept at 100° for another 4 minutes and then cooled to room temperature. The white needles which separated were filtered off (filtrate A), washed with a little acetic acid (yield, 0·38 g., 60%; m. p. 228—232°), and crystallised from ethanol (20 ml.), giving *N*-*acetyl*-N′-p-*chlorophenylurea*, needles, m. p. 231—232° (undepressed in admixture with material prepared as detailed below) (Found: C, 50·45; H, 4·4; N, 13·3. $C_9H_9O_2N_2Cl$ requires C, 50·8; H, 4·2; N, 13·2%). Filtrate A was poured into water (100 ml.), and the separated solid (0·40 g.) was fractionated, by means of ethanol, into the above acetylurea (0·13 g., hence total yield 80%), and the very soluble di-*p*-tolyl disulphide (0·21 g., 71% calc. according to eqn. 8), m. p. and mixed m. p. 46—47° (Found: C, 67·9; H, 5·5. Calc. for $C_{14}H_{14}S_2$: C, 68·3; H, 5·7%). The sulphenylurea was almost completely recovered after 5 minutes' treatment with the above reagent at 50°; more prolonged refluxing (20 minutes) caused complete decomposition.

(*b*) Analogous treatment of *N*-phenyl-*N*′-toluene-*p*-sulphenylurea (but pouring the entire reaction mixture into water, since direct crystallisation from acetic anhydride did not occur) gave *N*-acetyl-*N*′-phenylurea, m. p. 182—183°, and di-*p*-tolyl disulphide, in similar yields. N.B. Because of the closeness of the m. p.s of *N*-acetyl-*N*′-*p*-chlorophenylurea and *p*-chlorophenylacetylurea (m. p. 228—230°; Spielmann, Geiszler, and Close, *J. Amer. Chem. Soc.*, 1948, **70**, 4189) this additional hydrolysis was performed. The formation of the acetylated urea of known formula under identical conditions confirms the structure of *N*-acetyl-*N*′-*p*-chlorophenylurea.

N-*Acetyl*-N′-p-*chlorophenylurea*.—(*a*) A solution of *p*-chlorophenylurea (1·7 g., 0·01 mole) in acetic anhydride (18 ml.), treated with concentrated sulphuric acid (4 drops), was kept at 100° for 20 minutes, boiled briefly, kept at 100° for a further 20 minutes, and slowly added to water (120 ml.). The separated solid (m. p. 220—224°; 1·35 g., 64%) gave, after two crystallisations from boiling ethanol (60 ml.), *N*-acetyl-*N*′-*p*-chlorophenylurea, m. p. 231—232° (Found: N, 13·4%).

Heating *p*-chlorophenylurea (0·01 mole) with acetic anhydride (8 ml.) in pyridine (15 ml.) at 100° for ½—1 hour gave 3—5% of the acetyl derivative, most of the starting material being recovered, while longer treatment (4 hr.) resulted mainly in *p*-chloroacetanilide, m. p. 178—179°.

(*b*) *p*-Chlorophenylcyanamide (1·53 g., 0·01 mole) was added to acetic anhydride (15 ml.) and concentrated sulphuric acid (4 drops) at room temperature. The resulting hot solution deposited white needles of the product immediately. After 3 minutes' boiling, the liquid was poured into water (120 ml.) and the separated white solid (0·95 g., 45%) (filtrate A) crystallised from ethanol, yielding *N*-acetyl-*N*′-*p*-chlorophenylurea, m. p. 231—232°. The aqueous filtrates A were made alkaline with sodium hydroxide; the precipitate (0·45 g., 27%) was *p*-chloroacetanilide, m. p. 178—179° (from ethanol).

p-Tolylcyanamide gave 21% of *N*-acetyl-*N*′-*p*-tolylurea and 60% of *N*-acetyl-*p*-toluidine.

N-*Phenyl*-N′-*toluene*-p-*sulphonylurea*.—(*a*) To a solution of *N*-phenyl-*N*′-toluene-*p*-sulphinylurea (1·37 g., 0·005 mole) in 1·5% (w/v) aqueous sodium hydroxide (27 ml., 0·01 mole),

aqueous potassium permanganate (20 ml., 5% w/v) was rapidly added at room temperature. The excess of the oxidising agent was consumed with sodium sulphite, and the manganese dioxide filtered off. Acidification at 0° (microcrystalline precipitate, m. p. 164—170°; 1·35 g., *i.e.* 93%), and two recrystallisations from acetone–benzene–light petroleum (4 ml. each) gave *N*-phenyl-*N'*-toluene-*p*-sulphonylurea, m. p. 171—173° (undepressed by authentic material; *J.*, 1951, 1258) (Found: C, 58·3; H, 4·65. Calc. for $C_{14}H_{14}O_3N_2S$: C, 57·9; H, 4·8%).

(*b*) To a suspension of finely divided *N*-phenyl-*N'*-toluene-*p*-sulphenylurea (2·60 g., 0·01 mole) in aqueous sodium hydroxide (3% w/v; 40 ml.), potassium permanganate solution (5% w/v; 125 ml., 0·02 g.-atom of O) was added with shaking during 10 minutes, in 10 portions, at room temperature. The dark green liquid was set aside for 10 minutes, then treated with excess of sodium sulphite, and the precipitated manganese dioxide removed by filtration. Acidification of the filtrate gave a white flocculent solid (1·8 g., 62%). In order to oxidize any small quantity of sulphinylurea, this was redissolved in alkali and re-oxidized (15 ml.; 5% w/v). The product, isolated as before and crystallised from benzene, was *N*-phenyl-*N'*-toluene-*p*-sulphonylurea, m. p. and mixed m. p. 170—171° (Found: C, 58·2; H, 4·95%). Use of a large excess of oxidising agent causes oxidation of the sulphonylurea.

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112. *The Kinetics of the Oxidation of Ethylene by Nitrogen Dioxide.*

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The reaction between nitrogen dioxide and ethylene has been studied by the static method, the total pressure and the nitrogen dioxide concentration being followed for initial pressures of between 3 and 12 cm. Hg of the reactants. The pressure at high temperatures rises rapidly, whereas at low temperatures there is a pressure drop followed by a rise. The NO_2 concentration decreases monotonically throughout the reaction. Rates of reaction were measured by drawing tangents to the curves of $[NO_2]$ against time.

The results were systematised by considering the initial slope of the $[NO_2]$–time curve:

$$-(d[NO_2]/dt)_{t=0} = k_{III}[NO_2]^{1\cdot8}[C_2H_4]^{1\cdot8}$$

A plot of $\log_{10} k_{III}$ against $1/T$ gave two intersecting straight lines with equations:

$$k_{III} = 10^{8\cdot5} \exp(-12{,}500/RT)\ \text{l.}^3\ \text{mole}^{-3}\ \text{sec.}^{-1}\ (160—220°),$$
$$k_{III} = 10^{10\cdot9} \exp(-18{,}000/RT)\ \text{l.}^3\ \text{mole}^{-3}\ \text{sec.}^{-1}\ (220—280°).$$

The $[NO_2]$–t curve in the course of a run was approximately of first order, more nitrogen dioxide having disappeared at a given time than would be expected from the third-order law, presumably because it reacts further with a product of the initial reaction. The process governing the rate of pressure rise had an activation energy of 17,000 cal.

The gaseous products were almost entirely carbon dioxide, carbon monoxide, and nitric oxide. The other products included an oil and a small amount of carbon-like material. Addition of nitric oxide or of air had no effect on the kinetics of disappearance of nitrogen dioxide. Increasing the surface : volume ratio by a factor of 8 had no effect at high temperature, and only a slight effect at low temperatures.

These facts are consistent with the view that nitrogen dioxide adds on to ethylene in the molecular ratio of 2 : 1, and that this product decomposes to give fragments capable of reacting with further nitrogen dioxide with complete oxidation.

IN the combustion of organic nitrates, nitrogen dioxide is considered to be split off and to oxidise the other fragments (Phillips, *Nature*, 1947, **160**, 753; 1950, **165**, 564). Thus oxidation of organic compounds by nitrogen dioxide may be important in the chemistry of the propagation of reaction in nitrates. The oxidation of formaldehyde (Pollard and Wyatt, *Trans. Faraday Soc.*, 1949, **45**, 760, 767) has therefore already been studied.

Acetaldehyde (McDowell and Thomas, *ibid.*, 1950, **46**, 1030) and acetylene (Thomas, personal communication) have also been studied, although for other reasons. It was of interest to examine the oxidation of ethylene, as a representative olefin and because it has been suggested that ethylene formed by the unimolecular decomposition of nitroethane would be readily oxidised by nitrogen dioxide produced from the nitrous acid left after the initial stage of the decomposition (Cottrell, Graham, and Reid, *ibid.*, 1951, **47**, 1089).

Experimental

Materials.—Nitrogen dioxide, prepared by heating mixed lead nitrate and sand over which dry oxygen was flowing, was distilled several times over phosphoric oxide and stored at liquid-nitrogen temperature. Commercial ethylene was passed over phosphoric oxide and potassium hydroxide and distilled several times.

Apparatus.—The "Pyrex" reaction vessel of volume 500 cm.^{3} was heated in a vertical electrical furnace, controlled to $\pm 0{\cdot}1°$ by a "Sunvic" resistance thermometer controller. Temperature measurement was by calibrated chromel–alumel thermocouple. A glass spiral manometer (Yorke, *J. Sci. Instr.*, 1945, **22**, 196; 1948, **25**, 16), attached to the vessel by heated capillary tubing, was enclosed in a heated oil-bath. Pressures were read to $\pm 0{\cdot}02$ cm. of Hg, by use of a light source, mirror on the gauge, and scale. The furnace had windows through which a light beam was passed on to a photo-cell, whose output was balanced in a bridge circuit. The bridge reading was calibrated against the nitrogen dioxide concentration (McDowell and Thomas, *loc. cit.*).

The system was evacuated by a mercury diffusion pump. Nitrogen dioxide was admitted to the reaction vessel, the pressure and bridge reading being noted (thus checking the calibration of the photo-cell bridge circuit). Ethylene was then admitted during about 5 seconds and the reaction followed by noting the pressure and bridge reading. The products could be removed and admitted to a trap cooled in liquid nitrogen, which could warm to $-80°$, and the permanent gases could then be removed by a Töpler pump, either to a cell for infra-red spectroscopic examination or to a gas sampler for chemical analysis in a Bone and Wheeler apparatus.

Kinetic Results.—At 290° the kinetic results were not very reproducible, and at pressures of over 30 cm. explosions occurred. It was established in these runs that the pressure increase is proportional to the initial pressure of nitrogen dioxide, and is equal to $0{\cdot}45[NO_2]_{t=0}$, ethylene being present in excess. A few of the later runs at lower temperatures were continued sufficiently to check this. They agreed, except at the lowest temperatures where the pressure increase was less. Details of selected runs are given in Tables 1—3. In Table 1 are given the

Table 1. *Ethylene–nitrogen dioxide reaction. Details of selected runs.*

Run	Temp.	p-NO_2, cm.	p-C_2H_4, cm.	$(d[NO_2]/dt)_{t=0}$, cm./min.	k_{III}, cm.$^{-2}$ min.$^{-1}$	k_I, sec.$^{-1}$	Remarks
94	279·5°	5·87	5·68	8·0	$4{\cdot}1 \times 10^{-2}$	$5{\cdot}3 \times 10^{-3}$	
107	,,	5·98	2·12	3·4	4·5	4·8	
113	,,	5·86	10·56	14·2	3·9	5·4	
132	,,	1·96	5·88	0·95	4·2	—	
138	,,	7·96	5·99	16·0	4·2	5·5	
150	269·0	6·20	5·80	5·9	$2{\cdot}6_8 \times 10^{-2}$	$3{\cdot}2 \times 10^{-3}$	
151	,,	6·00	2·85	$2{\cdot}3_4$	$2{\cdot}6_6$	3·0	
153	,,	6·30	9·10	9·5	$2{\cdot}4_4$	$3{\cdot}1_5$	
172	,,	4·55	6·15	$3{\cdot}1_5$	$2{\cdot}3_4$	—	6·05 cm. of NO added
178	,,	3·31	11·89	4·0	$2{\cdot}3_9$	—	
179	,,	11·08	3·17	7·5	$2{\cdot}4_9$	—	
181	258·3	5·94	6·15	$4{\cdot}5_0$	$2{\cdot}0_6 \times 10^{-2}$	$2{\cdot}2_7 \times 10^{-3}$	
186	247·8	6·12	6·10	3·6	$1{\cdot}5_8 \times 10^{-2}$	$1{\cdot}96 \times 10^{-3}$	
189	,,	11·45	3·75	6·3	$1{\cdot}6_1$	$1{\cdot}7_7$	
193	,,	3·95	8·05	2·20	$1{\cdot}5_2$	$1{\cdot}8_9$	
197	233·9	6·25	6·22	$2{\cdot}2_5$	$9{\cdot}3 \times 10^{-3}$	—	
203	218·5	6·05	5·90	$1{\cdot}1_9$	$5{\cdot}5 \times 10^{-3}$	$6{\cdot}1 \times 10^{-4}$	
210	205·1	5·95	5·95	0·90	$4{\cdot}3 \times 10^{-3}$	$4{\cdot}3 \times 10^{-4}$	
212	,,	12·03	2·98	1·34	$4{\cdot}1_2$	2·8	
216	190·8	5·92	5·69	0·64	$3{\cdot}2 \times 10^{-3}$	—	
229	164·8	5·95	6·12	0·35	$1{\cdot}6_1 \times 10^{-3}$	—	
235	,,	20·05	9·90	$5{\cdot}3_8$	$1{\cdot}5_6$	—	
240	270·8	7·00	7·00	$8{\cdot}3_5$	$2{\cdot}4_8 \times 10^{-2}$	—	Packed reaction vessel
241	191·5	6·25	7·60	$1{\cdot}2_5$	$4{\cdot}0_6 \times 10^{-3}$	—	,, ,,
243	271·3	6·21	6·45	6·4	$2{\cdot}5_5 \times 10^{-2}$	—	Packed vessel, 6·20 cm. of air added

TABLE 2. *Ethylene–nitrogen dioxide reaction. Pressure–time data.*

Run	Δp (cm. Hg) at t (min.)													
t =	0	¼	½	¾	1	1½	2	3	4	6	8	10	20	
94	0·00	0·16	0·28	0·41	0·59	0·84	1·02	1·37	1·59	1·70	—	—	—	—
107	0·00	0·09	0·14	0·29	0·39	0·60	0·82	1·10	1·38	1·70	1·94	2·10	2·58	—
113	0·00	0·06	0·18	0·35	0·46	0·67	0·85	1·12	1·33	1·60	—	—	—	—
132	0·00	0·02	0·02	0·03	0·04	0·12	0·15	0·22	0·30	—	—	—	—	—
138	0·00	0·22	0·45	0·62	0·81	1·09	1·31	1·69	1·93	—	—	—	—	—
150	0·00	0·00	0·02	0·10	0·20	0·41	0·60	0·86	1·09	1·39	1·59	1·78	—	—
151	0·00	0·00	0·05	0·14	0·21	0·34	0·54	0·75	0·96	1·26	1·50	1·70	—	—
153	0·00	0·00	0·08	0·18	0·29	0·46	0·60	0·89	1·10	1·43	1·65	—	—	—
172	0·00	0·00	0·00	0·00	0·04	0·13	0·23	0·44	0·64	—	—	—	—	—
178	0·00	0·01	0·01	0·02	—	0·14	0·20	0·34	0·40	—	—	—	—	—
179	0·00	0·20	0·35	0·56	0·75	1·08	1·29	1·81	2·20	—	—	—	—	—
181	0·00	0·02	0·04	0·05	0·12	0·26	0·39	0·56	0·77	1·05	1·28	1·45	—	—

t =	0	½	1	1½	2	2½	3	4	5	6	8	10	20	60
186	0·00	0·00	0·05	0·11	0·22	0·31	0·40	0·59	0·71	0·86	1·06	1·26	—	—
189	0·00	−0·10	+0·01	0·19	0·39	0·55	0·70	0·99	1·25	1·51	1·92	2·29	—	—
193	0·00	−0·09	−0·09	−0·05	0·00	0·05	0·10	0·20	0·28	0·37	0·52	0·62	—	—
197	0·00	−0·21	−0·27	−0·30	−0·24	−0·21	−0·12	−0·02	0·09	0·23	0·42	0·58	1·22	2·15

t =	0	1	2	4	6	8	10	15	20	25	30	40	50	60
203	0·00	−0·38	−0·54	−0·53	−0·37	−0·23	−0·05	0·30	0·59	0·84	1·00	1·31	1·54	1·66

t =	0	1	2	4	7	10	15	20	30	40	60	80	100	120
210	0·00	−0·35	−0·59	−0·77	−0·80	−0·72	−0·48	−0·25	0·15	0·44	0·85	1·13	—	—
212	0·00	−0·49	−0·72	−0·91	−0·88	−0·69	−0·31	0·07	0·69	1·22	2·03	2·64	3·11	3·50
216	0·00	−0·31	−0·54	−0·88	−1·11	−1·21	−1·19	−1·11	−0·92	−0·50	−0·33	−0·07	0·15	—
229	0·00	−0·20	−0·39	−0·72	−1·10	−1·39	−1·67	−1·87	−2·05	−2·09	—	—	—	—
235	0·00	−2·45	−4·00	−5·45	−5·80	−5·31	−4·12	−3·06	−1·42	−0·46	+0·77	1·60	2·19	—

t =	0	¼	½	¾	1	1½	2	3	4	6	8	10	20	30
240	0·00	0·10	0·35	0·60	0·90	1·38	1·70	2·15	2·42	2·77	—	—	—	
241	0·00	—	−0·27	—	−0·42	−0·60	−0·70	−0·88	−0·93	−1·00	−1·00	—	−0·60	−0·26
243	0·00	0·05	0·22	0·41	0·60	0·88	1·12	1·36	—	—	—	—	—	—

TABLE 3. *Ethylene–nitrogen dioxide reaction.* $[NO_2]$–t *data.*

Run	$[NO_2]$, cm., at t (min.)													
t =	0	¼	½	¾	1	1¼	1½	1¾	2	2½	3	3½	4	5
94	$5{\cdot}8_5$	$4{\cdot}3_0$	$3{\cdot}0_2$	$2{\cdot}2_3$	$1{\cdot}6_0$	—	$1{\cdot}2_0$	—	$0{\cdot}9_0$	—	—	—	—	—
107	$6{\cdot}0_0$	$5{\cdot}4_0$	$4{\cdot}6_0$	4·1	3·8	3·3	3·0	2·8	2·6	—	—	—	—	—
113	5·8	3·2	1·8	1·2	0·8	0·7	—	—	—	—	—	—	—	—
132	$1{\cdot}9_5$	$1{\cdot}7_2$	$1{\cdot}4_9$	$1{\cdot}3_0$	$1{\cdot}1_0$	$0{\cdot}9_5$	$0{\cdot}8_5$	$0{\cdot}7_0$	$0{\cdot}5_5$	—	—	—	—	—
138	8·0	4·9	$3{\cdot}1_5$	$2{\cdot}3_0$	1·8	1·5	—	—	—	—	—	—	—	—
150	6·2	5·0	3·9	3·1	2·4	2·1	1·7	1·4	1·3	—	—	—	—	—
151	6·0	5·5	5·1	$4{\cdot}6_5$	$4{\cdot}1_5$	3·7	3·4	3·1	2·8	—	—	—	—	—
153	6·3	4·5	2·9	$2{\cdot}1_5$	$1{\cdot}5_5$	1·1	—	—	—	—	—	—	—	—
172	4·6	3·9	3·2	2·8	$2{\cdot}2_5$	1·9	$1{\cdot}6_5$	$1{\cdot}4_5$	1·3	—	—	—	—	—
178	3·3	2·4	$1{\cdot}7_5$	1·3	1·0	0·8	$0{\cdot}6_5$	$0{\cdot}5_5$	$0{\cdot}4_5$	—	—	—	—	—
179	11·1	$10{\cdot}0_5$	8·3	7·2	6·3	5·6	5·1	4·6	$4{\cdot}3_5$	$3{\cdot}8_5$	3·5	—	—	—
181	6·0	$5{\cdot}6_5$	$4{\cdot}1_5$	3·4	2·8	2·4	2·0	$1{\cdot}6_5$	$1{\cdot}4_5$	$1{\cdot}1_5$	1·0	—	—	—
186	6·1	5·3	4·6	3·9	$3{\cdot}3_5$	$2{\cdot}8_5$	$2{\cdot}4_5$	$2{\cdot}1_5$	$1{\cdot}8_5$	$1{\cdot}4_5$	1·2	—	—	—
189	11·5	10·3	9·1	8·0	$7{\cdot}1_5$	6·5	$5{\cdot}8_5$	$5{\cdot}4_5$	$5{\cdot}0_5$	4·4	4·0	—	—	—
193	$3{\cdot}9_5$	3·4	2·9	$2{\cdot}5_5$	2·2	$1{\cdot}9_5$	1·6	1·4	$1{\cdot}2_5$	$0{\cdot}9_5$	—	—	—	—
197	6·3	$6{\cdot}0_5$	5·6	5·1	4·6	$4{\cdot}1_5$	3·9	$3{\cdot}4_5$	$3{\cdot}1_5$	2·7	2·3	$2{\cdot}0_5$	$1{\cdot}7_5$	—
203	6·1	5·9	5·6	$5{\cdot}3_5$	5·1	$4{\cdot}8_5$	4·6	$4{\cdot}3_5$	4·1	3·7	3·3	$3{\cdot}0_5$	2·8	2·3

t =	0	½	1	1½	2	2½	3	3½	4	4½	5	6	8	10
210	6·0	5·6	5·3	4·9	4·6	4·2	3·9	3·7	3·4	3·2	3·0	2·7	2·2	—
212	12·0	11·5	10·9	$10{\cdot}3_5$	$9{\cdot}9_5$	9·5	9·1	8·8	$8{\cdot}4_5$	$8{\cdot}0_5$	$7{\cdot}8_5$	$7{\cdot}3_5$	$6{\cdot}6_5$	6·1
216	5·9	5·6	5·3	5·0	4·8	4·5	$4{\cdot}3_5$	4·2	4·0	3·8	3·6	3·4	$2{\cdot}9_5$	$2{\cdot}5_5$
229	$5{\cdot}9_5$	5·8	5·6	$5{\cdot}4_5$	5·3	5·2	5·1	5·0	4·9	$4{\cdot}7_5$	4·6	$4{\cdot}3_5$	4·0	$3{\cdot}6_5$
235	20·0	17·7	15·9	14·6	13·5	12·4	11·6	11·1	10·5	9·9	9·5	8·8	7·7	6·9

t =	0	¼	½	¾	1	1¼	1½	1¾	2	2½	3	3½	4	
240	7·0	5·3	3·9	2·8	2·3	1·8	1·6	1·3	1·1	—	—	—	—	—
241	6·3	—	5·7	—	5·2	—	4·9	—	4·5	4·2	3·9	3·7	3·5	—
243	6·2	4·8	3·7	2·9	2·5	2·0	1·7	1·5	1·4	—	—	—	—	—

temperature, the initial pressures of reactants, the initial slope of the $[NO_2]$–time curve, a third-order constant, and a first-order constant. In Table 2 are given the pressure–time data, and in Table 3 the $[NO_2]$–time data. At 279·5° the $[NO_2]$–time curves are not very satisfactory, because the reaction is too fast to follow accurately. The runs are numbered in chronological order. The results show that, although at higher temperatures the pressure increases with time, yet at lower temperatures there is a decrease followed by a rise. The NO_2 concentration decreases monotonically throughout the reaction. Typical runs are shown in Fig. 1. The pressure change is not simply related to the amount of NO_2 reacting, and thus the pressure–time curves may not be susceptible of a straightforward kinetic interpretation.

Apparently two reactions, addition of nitrogen dioxide (with pressure decrease) and oxidation (with pressure increase) are proceeding, either in series or in parallel, with different activation energies. Attempts at kinetic analysis were largely confined to the $[NO_2]$–time curves. Runs at 269° were first considered. The initial slope of the $[NO_2]$–time curve was obtained by plotting the readings, drawing tangents at various pressures of NO_2, and extrapolating back to the known original pressure. The initial slope depended on $[NO_2]^{1\cdot8}$ and $[C_2H_4]^{1\cdot2}$. The results at 279·5°, however, seemed to be better expressed by the simple powers 2 and 1. The non-integral powers may be due to a side reaction which is less important at high temperature.

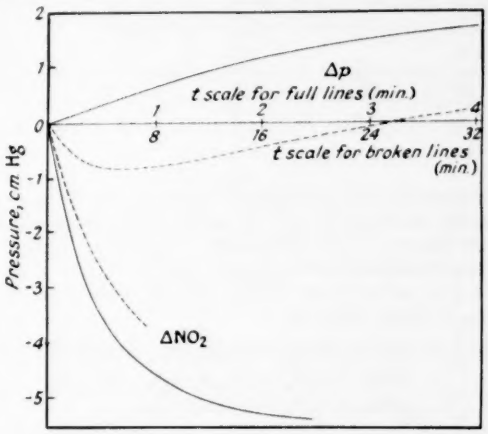

FIG. 1. *p–t and* $[NO_2]$*–t plots for run* 106 ———, *and run* 210 – – – –.

In Table 1 are given the constants obtained at all temperatures, it being assumed that $(-d[NO_2]/dt)_{t=0} = k_{III}[NO_2]^{1\cdot8}[C_2H_4]^{1\cdot2}$, except for 279·5°, where the powers 2 and 1 are used. The constancy of k_{III} for changes by a factor of 3 or 4 in the pressures of the reactants is good; clearly, the initial step is kinetically the same throughout the temperature range. This implies that the addition and oxidation reactions must take place in series.

A plot of $\log_{10} k_{III}$ against $1/T$ for all runs falls into two straight-line segments, which have the equations given on p. 556.

The slope of the $[NO_2]$–t curve was approximately proportional to the pressure of NO_2 during a run up to about 50% reaction, *i.e.*, $-d[NO_2]/dt = k'[NO_2]_t$, although of course k' depended on the initial pressures of NO_2 and ethylene. This apparent first-order rate of disappearance of NO_2 was checked by calculating first-order constants by using the integrated form of the first-order law. The " constants " decreased slightly as the reaction proceeded, except at the lowest temperatures, when the decrease was rapid. The approximation was less good for high and for low initial concentration of NO_2.

The vessel was packed with Pyrex capillary tubing to give an increase in the surface : volume ratio by a factor of 8. At high temperatures k_{III} was unchanged; at low temperatures it was increased by about 30%, showing that the surface effect is slight. Addition of NO (runs 170—172) and air (run 243) had little effect on k_{III}.

Although a simple molecular interpretation of the pressure–time curves was not expected, the part involving pressure increase was roughly of first order, as determined by Guggenheim's method (*Phil. Mag.*, 1926, **2**, 538). At high temperatures the maximum slope of the pressure–time curve was roughly proportional to the initial pressure of NO_2 only. In all these runs, the

ethylene was present in excess, so that the amount of an intermediate formed might be expected to be proportional to the initial pressure of NO_2. The first-order constants obtained from the pressure increase are given in Table 1 as k_I. The temperature dependence of k_I is given by $k_I = 10^{4\cdot35}e^{-17,000/RT}$ sec.$^{-1}$. For those runs in which the NO_2/C_2H_4 ratio is large, k_I is smaller than usual. These results were not included in the activation-energy plot.

Whereas the addition of NO had no effect on the $[NO_2]$–t curves, yet it had a marked effect on the pressure–time curve, causing an apparent induction period before the pressure started to increase.

Stoicheiometry and Analyses.—Where there was no initial pressure drop the total pressure increase of 45% of the initial pressure of NO_2 may be compared with a 50% pressure increase calculated for $6NO_2 + C_2H_4 \longrightarrow 2CO_2 + 2H_2O + 6NO$. As mentioned above, the pressure increase is not simply related to the change in NO_2 pressure. In the runs at low temperature, where there is an initial pressure decrease, the ratio of the initial slope of the $[NO_2]$–t curve to the initial slope of the pressure–time curve was noted (Table 4). At temperatures immediately

TABLE 4. *Ratio of* $(d[NO_2]/dt)_{t=0}$ *to* $(dp/dt)_{t=0}$ *for various runs.*

Run	Temp.	Ratio	Mean	Run	Temp.	Ratio	Mean
203	218·5°	2·4		210	205·1°	2·0	
204	,,	2·6		211	,,	2·0	
207	,,	2·6	2·60	212	,,	2·0	2·03
208	,,	2·5		213	,,	2·1	
209	,,	2·9		214	,,	2·1	
229	164·75	1·8		215	,,	2·0	
230	,,	1·8	1·72	216	190·75	2·1	
233	,,	1·7		218	,,	1·9	1·93
235	,,	1·6		221	,,	1·8	

above those for which results are given in the Table, the pressure decrease was too rapid to be measured accurately, and at even higher temperatures it was not observed. The ratio is greater the higher the temperature. There are only a few possible addition compounds, so the number of simple equations which can be written to explain the pressure drop is small. Three which give products for which there is evidence at lower temperatures (cf. Levy, Scaife, and Smith, *J.*, 1946, 1096) are

$$2NO_2 + C_2H_4 \longrightarrow C_2H_3{\cdot}NO_2 + \tfrac{1}{2}(H_2O + NO + NO_2) \quad \Delta[NO_2]/\Delta p = 3$$
$$2NO_2 + C_2H_4 \longrightarrow C_2H_3{\cdot}NO_2 + HNO_2 \quad \Delta[NO_2]/\Delta p = 2$$
$$2NO_2 + C_2H_4 \longrightarrow C_2H_4(NO_2)_2 \quad \Delta[NO_2]/\Delta p = 1$$

Presumably formation of nitroethylene is favoured at higher temperatures, whereas formation of dinitroethane (the structure being unspecified for the present) is favoured at lower temperatures.

Direct interpretation of these p–t results in terms of such equations is not quantitatively possible because of side reactions. Polymerisation of nitroethylene might well take place, causing a smaller value of $\Delta[NO_2]/\Delta p$, and in addition the results of gas analyses show that some complete oxidation has taken place even at very short times, which would cause a larger value of $\Delta[NO_2]/\Delta p$ than expected.

Qualitative analysis by infra-red spectroscopy of the gaseous products showed carbon dioxide, carbon monoxide, nitric oxide, and unchanged ethylene. Particularly at the lower temperatures, the products when removed for analysis contained a high-boiling oil, which was not analysed, but was thought to be a mixture of nitroethylene, dinitroethane, and possibly nitroethyl nitrite. A deposit of dark material was gradually formed in the tubes leading to the reaction vessel. The gaseous products were analysed in the Bone and Wheeler apparatus for carbon dioxide, nitric oxide, ethylene, and carbon monoxide, potassium hydroxide, ferrous sulphate, silver sulphate and concentrated sulphuric acid, and ammoniacal cuprous chloride being used as absorbents. The residue was generally 2—3% and never more than 5%. There is some interaction between these reagents, and at the times of greatest interest, near the beginning of the reaction, the samples were small, so that the results were not very reproducible. Accordingly, only a few analyses were carried out, all for runs at 190·6°, with 10 cm. of NO_2 and 5 cm. of C_2H_4. After short times (1—2 minutes) the permanent gas contained carbon dioxide and carbon monoxide in the ratio of about 5 : 1, nitric oxide roughly equivalent to the oxides of carbon, and unchanged ethylene. The NO analyses were particularly variable because of the

possibility of carrying a small amount of NO_2 over into the Töpler pump, where it would react to give NO. Typical results for the composition of the permanent gas are given in Table 5:

TABLE 5. *Typical compositions of permanent-gas products from reaction of* 10 *cm. of* NO_2 *and* 5 *cm. of* C_2H_4 *at* 190·6°.

Time stopped	CO_2, %	NO, %	C_2H_4, %	CO, %
1½ min.	4·5	14·1	75·0	1·0
1½ min.	4·0	19·5	73·4	0·9
2 min.	5·4	14·5	74·0	1·1

the residue was not analysed, and probably consisted of nitrogen with possibly a little nitrous oxide. No attempt was made to refine the method of analysis because products are likely to be too complex.

DISCUSSION

The results suggest that 2 mols. of nitrogen dioxide are added to one of ethylene, a process which can take place in two different ways with activation energies of approximately 18 and 12·5 kcal. to give an addition product which decomposes, possibly with nitroethylene as an intermediate, to fragments which are completely oxidised by more nitrogen dioxide. The process controlling the oxidation has an activation energy of about 17 kcal.

In discussing the initial rate of reaction of NO_2, it will be assumed that the main process is of the second order in NO_2 and the first order in ethylene, although the exact figures are 1·8 and 1·2. Two mechanisms for an apparent third-order reaction suggest themselves, as follows:

Scheme I	$NO_2 + C_2H_4$	$\longrightarrow NO_2{\cdot}C_2H_4$	(1)
	$NO_2{\cdot}C_2H_4$	$\longrightarrow NO_2 + C_2H_4$	(2)
	$NO_2 + NO_2{\cdot}C{\cdot}H_4$	$\longrightarrow C_2H_4(NO_2)_2$	(3)
Scheme II	$NO_2 + NO_2$	$\longrightarrow N_2O_4$	(4)
	N_2O_4	$\longrightarrow NO_2 + NO_2$	(5)
	$N_2O_4 + C_2H_4$	$\longrightarrow C_2H_4(NO_2)_2$	(6)

Applying the usual stationary state assumption to $NO_2{\cdot}C_2H_4$, we find that Scheme I gives

$$-\mathrm{d}[NO_2]/\mathrm{d}t = 2k_1k_3[NO_2]^2[C_2H_4]/(k_2 + k_3[NO_2])$$

and applying it to N_2O_4, we find that Scheme II gives

$$-\mathrm{d}[NO_2]/\mathrm{d}t = 2k_4k_6[NO_2]^2[C_2H_4]/(k_5 + k_6[C_2H_4])$$

Hence, in each scheme if the second term in the denominator is small compared to the first, third-order kinetics are obtained. If the second term has an effect in Scheme I, the dependence on NO_2 might be slightly less than on the second power, whereas in Scheme II the ethylene dependence might be slightly less than the first power. Thus Scheme I is to be preferred on these grounds.

The experimental activation energy is 12·5 kcal. at low temperatures and 18·0 kcal. at higher temperatures. Scheme I gives the activation energy as $E_1 + E_3 - E_2$; E_2 and E_3 might be expected to be small, so that the overall activation energy is expected to be $\sim E_1$. The reaction (1) involves the formation of a C–N bond and the conversion of a C=C bond into a C–C bond. The bond energies given by Coates and Sutton (*J.*, 1948, 1187) being used, this reaction should be exothermic to the extent of about 10 kcal., so there is no energetic reason why E_1 should not be 12—18 kcal. Scheme II gives the activation energy as $E_4 + E_6 - E_5$; $E_4 - E_5$ is known to be about −13 kcal. (Richards and Reid, *J. Chem. Physics*, 1933, **1**, 114), so the overall activation energy, $E = E_6 - 13$ kcal. Thus E_6 must be 25—31 kcal. if Scheme II is correct. Reaction (6) is certainly exothermic, though this seems perhaps rather a high value for E_6.

The experimental frequency factors are $10^{8.5}$ and $10^{10.9}$ $l.^2$ $mole^{-2}$ $sec.^{-1}$. Scheme I makes the overall factor the product of two bimolecular factors divided by the unimolecular factor for reaction (2). If the factor for reactions (1) and (3) is equal to the collision

frequency, then the numerator is 10^{20}—10^{24}, and the denominator 10^{12}—10^{14}. This allows the overall frequency factor to be between 10^6 and 10^{12}. The experimental values lie within this range, but surprisingly high in it; in many reactions involving NO_2 the bimolecular frequency factor is appreciably less than the collision number. This could be accounted for if the frequency factor for unimolecular radical decompositions were less than that usually found for molecules, and there is some evidence of this (cf. Howlett, *Trans. Faraday Soc.*, 1952, **48**, 25). Scheme II gives a similar result, but here the frequency factor of (5) is known to be at the high end of the range for unimolecular frequency factors (Richards and Reid, *loc. cit.*), and thus the overall factor is likely to be lower than that for Scheme I if it is assumed that all the bimolecular reactions have the same frequency factors. Since the experimental frequency factor is if anything rather high, this examination favours Scheme I.

A further support for Scheme I lies in the possibility of explaining the two activation energies of the reaction. The O–N–O molecule can form either a C–N bond or a C–O bond when adding to a carbon atom, and it is not to be expected that these two processes will have the same activation energies or frequency factors. That both modes of addition are possible has been shown by the Billingham workers who have obtained nitroethyl nitrate and dinitroethane from the reaction between nitrogen dioxide and ethylene (Levy, Scaife, and Smith, *loc. cit.*). It is also significant that in the reaction between nitrogen dioxide and formaldehyde, in which addition is also postulated, there are also two activation energies which might be explained similarly. On the other hand, if N_2O_4 is a symmetrical plane molecule of the formula $\begin{matrix}O\\O\end{matrix}\!\!>\!N\!-\!N\!<\!\!\begin{matrix}O\\O\end{matrix}$ as is suggested by spectroscopic (cf. Herzberg, "Infra Red and Raman Spectra," New York, 1945) and *X*-ray (Broadley and Robertson, *Nature*, 1949, **164**, 915) evidence, then it is much less easy to see how addition could take place in two different ways. Also, it is not possible to see how N_2O_4 would add on to ethylene even in one way, except by breaking and forming several bonds in the one putatively elementary step.

The relation between the initial rates of disappearance of NO_2 and of pressure decrease shown in Table 4 points to the formation of nitroethylene, probably by decomposition of nitroethyl nitrite. The nitroethylene formation appears to be temperature-dependent and to become the main reaction by about 220°, the temperature at which there appears to be a break in the activation energy curve. To take this into account, reaction Scheme I would have to consist of reactions (1), (2), and (3) as before, with the addition of

$$NO_2 + NO_2{\cdot}C_2H_4 \longrightarrow C_2H_4(O{\cdot}NO)(NO_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3a)$$

$$C_2H_4(O{\cdot}NO)(NO_2) \longrightarrow C_2H_3{\cdot}NO_2 + \tfrac{1}{2}(H_2O + NO + NO_2) \quad . \quad . \quad . \quad . \quad (7)$$

The compounds in parentheses are assumed to result from the decomposition of HNO_2.

This gives, with the obvious stationary-state assumptions,

$$\frac{-\,d[NO_2]}{dt} = \frac{k_1(2k_3 + k_{3a})[NO_2]^2[C_2H_4]}{k_2 + (k_3 + k_{3a})[NO_2]}$$

a relation of precisely the same form as before, and one which should lead to an activation energy plot with different slopes in the regions corresponding to the predominance of reaction (3) and of reaction (3*a*). With these activation energies not very different, a sharply segmented plot would not be expected, and the true activation energies and frequency factors would differ slightly from those deduced simply by drawing two straight lines through the experimental points. This consideration, which applies equally to the work of Pollard and Wyatt on formaldehyde (*loc. cit.*), makes only a slight difference to the numerical values and does not affect the argument.

Although the experimental results could probably be fitted to a smooth curve in the region of intersection of the straight lines actually drawn, in neither set is the precision sufficiently great to justify this procedure. Exactly similar kinetic results would follow if the mechanism of formation of nitroethylene involved hydrogen abstraction, as in (3*b*):

$$C_2H_4{\cdot}NO_2 + NO_2 \longrightarrow C_2H_3{\cdot}NO_2 + HNO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3b)$$

The subsequent apparent first-order decrease of NO_2 with time in any given run can be explained on the view that it is reacting further with fragments from the decomposition of the addition compounds. It is not possible to put forward a detailed scheme for this, as the number of possible intermediates is large, but that such a scheme could in principle explain the results was shown by the numerical solution * of the differential equations describing the reactions

$$2A + B \longrightarrow C \ (8); \quad A + C \longrightarrow D \ (9)$$

Here A and B are nitrogen dioxide and ethylene, and C may be a series of intermediates the last member of which reacts with nitrogen dioxide. In Fig. 2 are plotted the experimental results for the disappearance of NO_2 in run 203 (for example) and the theoretical curves corresponding to

$$-da/dt = ka^2b \text{ (3rd order)}$$

and

$$-da/dt = ka_0b_0a \text{ (1st order with same initial slope)}$$

Here concentrations are indicated by lower case letters, the subscript 0 referring to zero time. Also shown is the curve corresponding to the system of equations (8) and (9) with $\kappa = 6\ k_9/k_8b_0 = 80$.

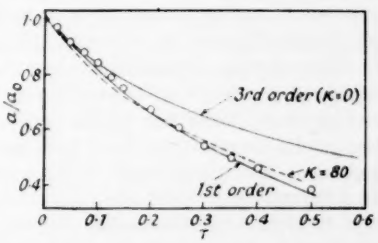

FIG. 2. *Showing apparent first-order decrease of* NO_2: o *experimental points for run* 203.

(The time scale is dimensionless, $\tau = k_8a_0b_0t$.) This curve fits the results fairly well. The rate constant for the second-order reaction (k_9) may be obtained from κ since k_8 (the third-order rate constant) is known from the initial slope; this gives a value for k_9 of approximately 10 l. mole^{-1} sec.$^{-1}$ which, if combined with an activation energy of 17,000 cal., gives a frequency factor of $10^{8\cdot5}$ l. mole^{-1} sec.$^{-1}$, a reasonable value for a second-order reaction frequency factor.

The " first-order rate constant " characterising the pressure rise cannot be interpreted on a molecular basis. The low frequency factor ($10^{4\cdot35}$ compared with 10^{13} for a unimolecular reaction) shows that the process is not a simple first-order reaction, as also does the fact that the " constant " decreases when $[NO_2]/[C_2H_4]$ is large. The process has an activation energy of 17 kcal., which is not very different from that found for the oxidation of aldehydes by nitrogen dioxide.

The mechanism put forward above is very similar to that suggested by Pollard and Wyatt (*loc. cit.*) for the oxidation of formaldehyde. Although the latter is kinetically of the second order, this could be so if, in Scheme I, $k_2 < k'_3[NO_2]$ for the analogous reactions with formaldehyde. The " dinitro " derivative of formaldehyde would probably not exist as such. On the other hand, McDowell and Thomas (*loc. cit.*) favour hydrogen abstraction as the initial reaction of nitrogen dioxide with aldehydes. Hydrogen abstraction is unlikely as a mechanism for the ethylene reaction, both because of the experimental evidence on the pressure and because the C–H bond in ethylene is much stronger than C–H bond in formaldehyde. Addition has also been shown to be the probable first step.

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* The authors are indebted to Mr. N. Ream for the numerical solution, which was obtained by using the differential analyser at the Butterwick Research Laboratories.

113. *The Preparation of* 2 : 3-*Anhydromethyl*-D-*lyxoside from* 2-*Toluene*-p-*sulphonyl Methyl*-D-*xylofuranoside, and Synthesis of* 2-*Methyl* D-*Xylose,* 3-*Methyl* D-*Arabinose, and* 3 : 5-*Dimethyl* D-*Arabinose.*

By E. E. Percival and Rolf Zobrist.

Crystalline 2 : 3-anhydromethyl-D-lyxoside has been prepared; hydrolysis of the anhydro-ring with sodium methoxide led to the isolation and characterisation of crystalline 2-methyl D-xylose and syrupy 3-methyl D-arabinose.

Methylation of the anhydro-compound gave crystalline 5-methyl 2 : 3-anhydromethyl-D-lyxoside. Fission of the anhydro-ring, followed by hydrolysis of the glycosidic methoxyl group, gave only one dimethyl pentose which has been identified as 3 : 5-dimethyl D-arabinose.

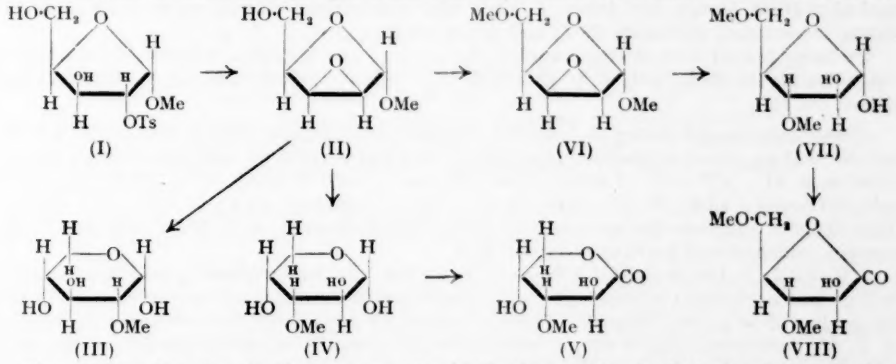
Earlier work (Haworth, Hirst, and Panizzon, *J.*, 1934, 154; Peat and Wiggins, *J.*, 1938, 1088) furnished evidence that the alkaline hydrolysis of toluene-*p*-sulphonyl groups from methylglucosides results in the formation of ethylene oxide rings provided that there is a free hydroxyl group, in the *trans*-position, on the carbon atom adjacent to that carrying the toluenesulphonyl group. If these conditions prevail hydrolysis is accompanied by Walden inversion on the carbon atom which formerly carried the toluenesulphonyl residue. If was also shown by these workers that scission of the oxide ring with sodium methoxide gives two products. The ring can apparently break on either side of the oxygen atom, and at the point of entry of the methoxy-group inversion takes place. It is not always possible to isolate both products, since the proportions vary, that is, the chances of the two oxygen bridges being split are not equal in all such compounds owing to steric factors.

We decided to investigate some of these steric effects and at the same time attempt to synthesise different methylated derivatives of pentoses and methylpentosides. 2-Toluene-*p*-sulphonyl methyl-D-xylofuranoside (I) was used as the starting material. Hydrolysis with alkali gave 2 : 3-anhydromethyl-D-lyxoside (II) and fission of the anhydro-ring gave 2-methyl D-xylose (III) and syrupy 3-methyl D-arabinose (IV) in the ratio of 1 : 2. 2-Methyl xylose had m. p. 134°, not depressed on admixture with an authentic specimen, and on treatment with ethanolic aniline yielded the characteristic anilide (Percival and Willox, *J.*, 1949, 1608). 3-Methyl D-arabinose was a colourless syrup, $[\alpha]_D$ −90° (*c*, 0·84 in H_2O) (initial). Oxidation with bromine water gave a crystalline lactone (V), m. p. 81°, which on treatment with methyl-alcoholic ammonia gave a crystalline amide, m. p. 132°. Hirst, Jones, and Williams (*J.*, 1947, 1062) record m. p. 78° and m. p. 132° for the same derivatives from 3-methyl L-arabinose.

2 : 3-Anhydromethyl-lyxoside was methylated with a view to ascertaining whether a 5-methoxyl group would influence the fission of the oxide ring. Treatment of crystalline 5-methyl 2 : 3-anhydromethyl-lyxoside (VI) with sodium methoxide gave a syrup containing only one dimethyl pentose, 3 : 5-dimethyl D-arabinose, contaminated with traces of trimethyl, monomethyl, and unmethylated pentoses. No evidence for the presence of 2 : 5-dimethyl xylose could be obtained.

Similar treatment of syrupy 2 : 3-anhydromethyl-lyxoside gave an identical syrup. These syrups were combined and freed from traces of impurity by separation on a column of powdered cellulose. Demethylation and chromatographic analysis of the resulting syrup revealed only the presence of arabinose and partially methylated arabinose. No xylose or methylated xyloses could be found. The pure dimethyl pentose separated from the column was identified as 3 : 5-dimethyl D-arabinose (VII) by oxidation with bromine water to the corresponding dimethyl D-arabonolactone (VIII). This lactone was crystalline (m. p. 74—75°) and its slow rate of mutarotation in aqueous solution ($[\alpha]_D$ +85° changing to +57° in 27 days) indicated that it belonged to the γ-series of arabonolactones (cf. Smith and Cunneen, *J.*, 1948, 1146, who record m. p. 75°, $[\alpha]_D$ −84° changing to −69° in 28 days for 3 : 5-dimethyl L-arabonolactone), and it gave a crystalline phenylhydrazide (Hirst, Jones and Williams, *loc. cit.*). The possibility of the simultaneous formation of 2 : 3- and 2 : 5-anhydromethyl-lyxosides had been envisaged, but no proof of the presence of

fission products from the 2 : 5-ring compound could be obtained. It is conceivable, however, that part of the 2-methyl xylose isolated might have been derived from this source.



It is interesting that in the absence of substitution on $C_{(5)}$ hydrolysis of the ethylene oxide compound caused fission of both oxygen bridges and the two expected monomethyl derivatives, 2-methyl D-xylose and 3-methyl D-arabinose, were isolated. However, when a methyl group occupied $C_{(5)}$ a preferential splitting of the ring occurred between the oxygen atom and $C_{(3)}$, and only 3 : 5-dimethyl D-arabinose was obtained. No trace of the other isomer, 2 : 5-dimethyl D-xylose, could be found. Similar results have been obtained with methylated anhydro-derivatives of rhamnose and of fucose (unpublished work).

Experimental

2 : 3-*Anhydromethyl*-D-*lyxoside*.—2-Toluene-*p*-sulphonyl methylxylofuranoside (24 g.) (Percival and Zobrist, *J.*, 1952, 4306) was dissolved in ethanol (400 c.c.) and hydrolysed with 2N-sodium hydroxide at 75° until permanently pink to phenolphthalein (36·3 c.c., 96%). The solvents were removed under diminished pressure. Repeated extraction of the residue with ethyl acetate and removal of the solvent gave a syrup (11 g.) which partly crystallised. The crystals (A) (2·7 g., 23%) were separated and after recrystallisation from benzene had m. p. 81°, $[\alpha]_D^{15}$ +57° (*c*, 1·0 in H_2O) (Found : C, 49·3; H, 6·5; OMe, 20·7. $C_6H_{10}O_4$ requires C, 49·3; H, 6·85; OMe, 21·2%). The residual syrup (B) (8·3 g.) had $[\alpha]_D^{15}$ +4° (*c*, 0·95 in H_2O) (Found : OMe, 20·5%).

Alkaline Hydrolysis of 2 : 3-*Anhydromethyl*-D-*lyxoside*.—Crystalline 2 : 3-anhydromethyl-D-lyxoside (A) (0·1 g.) was heated at 95° for 12 hours with methanol (5 c.c.) containing 4% of sodium. Thereafter, the solution was diluted with water (5 c.c.), neutralised with solid carbon dioxide, and evaporated to dryness. Extraction with chloroform and removal of the solvent gave a colourless syrup. This was hydrolysed at 100° with 0·1N-sulphuric acid (10 c.c.) until no further change in rotation occurred ($[\alpha]_D^{15}$ +63° ⟶ −4·7° in 3 hours). Neutralisation of the solution with barium carbonate and evaporation to dryness gave a colourless syrup (C). Examination on a paper chromatogram with butanol–ethanol–water (4 : 1 : 5) revealed the presence of 2-methyl xylose (R_G 0·38), a second nomomethyl pentose (R_G 0·26), and unmethylated pentose (R_G 0·19).

The residual syrup (B) (6·0 g.) was hydrolysed as described for the crystalline material (A) and, after removal of the glycosidic methoxyl group, gave a pale yellow syrup (D) (4·1 g.). Comparison on a paper chromatogram of the spots given by this syrup with those given by syrup (C) showed the two syrups to be identical. The above results together with the difference in rotation suggest that the crystals (A) are the α-form of 2 : 3-anhydromethyl-D-lyxoside and that the residual syrup (B) is a mixture of the α- and the β-form of this sugar.

The syrups (C) and (D) (4·0 g.) were combined and separated on a column of powdered cellulose (Chanda, Hirst, and Percival, *J.*, 1951, 1240). Elution was by purified light petroleum (b. p. 100—120°)–*n*-butanol (1 : 9) saturated with water. Fraction 1 (1·05 g.) was crystalline 2-methyl xylose, m. p. 134°, unchanged on admixture with an authentic specimen, $[\alpha]_D^{15}$ −22° (initial), +26° (3 days) (*c*, 0·61 in H_2O) (cf. Percival and Willox, *loc. cit.*) (Found : C, 44·1; H, 7·4; OMe, 18·5. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3; OMe, 18·9%). Fraction 2 (2·16 g.) was syrupy 3-*methyl* D-*arabinose*, $[\alpha]_D^{15}$ −90° (initial), −43° (3 days) (*c*, 0·84 in H_2O) (Found : OMe, 18·6. $C_6H_{12}O_5$ requires OMe, 18·9%). Hirst, Jones, and Williams (*loc. cit.*) record

+110° (*c*, 3·6 in H_2O) for 3-methyl L-arabinose. Aqueous extraction of the column and removal of the water gave a syrup (0·4 g.). Quantitative determination of the sugars present by the method of Hirst, Hough, and Jones (*J.*, 1949, 928) with butanol–ethanol–water (4 : 1 : 5) as the eluting solvent gave arabinose (78%) and xylose (22%).

On being heated with alcoholic aniline (0·15 g. in 5 c.c.) 2-methyl D-xylose (0·1 g.) gave a crystalline aniline compound, m. p. 125—126°, $[\alpha]_D$ +212° (*c*, 0·5 in EtOAc) (cf. Percival and Willox, *loc. cit.*).

Characterisation of 3-*Methyl* D-*Arabinose.*—3-Methyl D-arabinose (0·23 g.) was oxidised to the lactone (0·13 g.), which crystallised immediately and was purified by sublimation in a vacuum; it had m. p. 81°, $[\alpha]_D^{18}$ +99° (5 min.), +104° (30 min.), +80° (3 days), +75° (22 days) (*c*, 2·994 in H_2O) (Found : 43·9; H, 6·7; OMe, 19·1. $C_6H_{10}O_5$ requires C, 44·4; H, 6·2; OMe, 19·1%). With alcoholic ammonia the *lactone* gave 3-methyl D-arabonamide, m. p. 132° (from alcohol and acetone), which gave a positive Weerman test.

5-*Methyl* 2 : 3-*Anhydromethyl-lyxoside.*—Crystalline 2 : 3-anhydromethyl-D-lyxofuranoside (0·60 g.) was methylated 3 times with methyl iodide and silver oxide, and a very volatile crystalline product (0·56 g.) was isolated. This was purified by sublimation in a vacuum and then had m. p. 43° (constant), $[\alpha]_D^{18}$ +60° (*c*, 4·45 in MeOH) (Found : C, 50·8; H, 7·7; OMe, 36·7. $C_7H_{12}O_4$ requires C, 52·5; H, 7·65; OMe, 38·7%).

Methylation of the syrupy 2 : 3-anhydromethyl-lyxofuranoside ($[\alpha]_D$ +4°) (6·0 g.) gave syrupy 5-methyl 2 : 3-anhydromethyl-D-lyxoside (5·5 g.), $[\alpha]_D^{18}$ +24° (*c*, 1·2 in H_2O) (Found : OMe, 39·5%).

Alkaline Hydrolysis of 5-*Methyl* 2 : 3-*Anhydromethyl*-D-*lyxoside.*—Following the procedure used for the unmethylated material, crystalline 5-methyl 2 : 3-anhydromethyl-lyxoside (0·40 g.) was treated with 4% sodium methoxide solution (25 c.c.). Neutralisation, however, was effected by passage through a column of cation exchange resin (Amberlite I.R.-100H). Evaporation of the solvents gave a colourless syrup (0·26 g.), $[\alpha]_D^{18}$ +64° (*c*, 0·92 in H_2O) (Found : OMe, 47·3. Calc. for $C_8H_{16}O_5$: OMe, 48·45%).

This syrup (0·25 g.) was hydrolysed with N-sulphuric acid at 100° for 1 hour, by which time the rotation had changed to $[\alpha]_D^{20}$ +37° (constant). After neutralisation and evaporation of the solvent a yellow syrup (E) (0·18 g.) was obtained. Chromatographic examination of this syrup with *n*-butanol–ethanol–water (4 : 1 : 5) indicated one main spot (R_G 0·77) and very faint spots corresponding to a trimethyl pentose (R_G 0·94), 2-methyl xylose (R_G 0·38), 3-methyl arabinose (R_G 0·27), and a pentose (R_G 0·19). 2 : 4-Dimethyl xylose, 2-methyl xylose, and xylose were run on the paper as controls.

Hydrolysis of syrupy 5-methyl 2 : 3-anhydromethyl-lyxoside ($[\alpha]_D$ +24°) (5·4 g.) with sodium methoxide gave a yellow syrup (3·8 g.), $[\alpha]_D^{18}$ −17° (*c*, 1·0 in H_2O) (Found : OMe, 47·4. Calc. for $C_8H_{16}O_5$: OMe, 48·45%). Hydrolysis with sulphuric acid gave a syrup (1·8 g.), $[\alpha]_D$ +38°, which revealed the same spots on a paper chromatogram as those given by the syrup (E) obtained from crystalline 5-methyl 2 : 3-anhydromethyl-lyxoside. Purification by passage through a column of powdered cellulose with light petroleum (b. p. 100—120°)–butanol (50 : 50) saturated with water as eluant gave a dimethyl pentose (F) (1·1 g.), $[\alpha]_D^{18}$ +47° (*c*, 0·76 in H_2O; const.) (Found : OMe, 33·9. $C_7H_{14}O_5$ requires OMe, 34·8%).

The purified syrup (F) (0·01 g.) was demethylated by hydriodic acid (1 c.c.) at 100° for 10 minutes. The solution was diluted with water (10 c.c.) neutralised with silver carbonate and filtered. Silver ions were removed by treatment with cation exchange resin (Amberlite I.R.-100H), and the solution was concentrated. Examination on a paper chromatogram with butanol–pyridine–water–benzene (5 : 3 : 3 : 1) as eluant revealed the presence of arabinose and unchanged dimethyl pentose. There was no evidence for the presence of xylose.

Characterisation of 3 : 5-*Dimethyl* D-*Arabinose.*—The sugar (F) (120 mg.) was oxidised with bromine (1 c.c.) in water (5. c.c.) at 20° for 48 hours. The 3 : 5-*dimethyl* D-*arabonolactone* (98 mg.) isolated in the usual way crystallised. The crystals, after recrystallisation from ether, had m. p. 74—75°, $[\alpha]_D^{18}$ +85° (after 15 min., *c*, 0·40 in H_2O), +80° (3 days), +77° (6 days), +57° (27 days) (Found: C, 47·4; H, 6·95; OMe, 34·9. $C_7H_{12}O_5$ requires C, 47·7; H, 6·9; OMe, 35·2%). A portion of the lactone (50 mg.) was heated with alcoholic phenylhydrazine for 2 hours. On cooling, the phenylhydrazide was deposited, as plates, m. p. 144—145°.

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114. *The Structure of Stachyose.*

By R. A. Laidlaw and (Miss) Clare B. Wylam.

Stachyose from soya-bean meal, on methylation and hydrolysis, yielded tetramethyl D-fructofuranose, tetramethyl D-galactopyranose, 2 : 3 : 4-trimethyl D-galactose, and 2 : 3 : 4-trimethyl D-glucose in equimolecular proportions. These results confirm the structure of stachyose as 6''-α-D-galactopyranosyl-6'-α-D-galactopyranosyl-2-α-D-glucopyranosyl-β-D-fructofuranoside.

The non-reducing tetrasaccharide stachyose, first isolated from *Stachys tubifera* by von Planta and Schulze (*Ber.*, 1890, **23**, 1692), was studied by Onuki (*J. Agric. Chem. Soc., Japan*, 1932, **8**, 445; 1933, **9**, 90; *Proc. Imp. Acad., Tokyo*, 1932, **8**, 496). Mild hydrolysis yielded fructose and a reducing trisaccharide, manninotriose, which on oxidation followed by methylation and hydrolysis gave 2 : 3 : 5 : 6-tetramethyl D-gluconic acid, 2 : 3 : 4-trimethyl D-galactose, and tetramethyl D-galactopyranose. Methylation and hydrolysis of stachyose itself yielded tetramethyl D-fructopyranose, tetramethyl D-galactopyranose, 2 : 3 : 4-trimethyl D-galactose, and a fraction presumed to be 2 : 3 : 6-trimethyl D-glucopyranose, which on complete methylation gave tetramethyl D-glucopyranose. With diazouracil stachyose gives a colour which is believed to be specific for the sucrose linkage (Raybin, *J. Amer. Chem. Soc.*, 1933, **55**, 2603; 1937, **59**, 1402; Purves and Hudson, *ibid.*, 1934, **56**, 709), and fructose is liberated by the action of invertase (Adams, Richtmyer, and Hudson, *J. Amer. Chem. Soc.*, 1943, **65**, 1369). It was also shown that both stachyose and manninotriose were hydrolysed by α-galactosidase, indicating that the linkages of both the galactose residues in the molecule were of the α-form. From the above information it appeared, therefore, that stachyose was 6''-α-D-galactosyl-4'-α-D-galactosyl-2-α-D-glucosyl-β-D-fructoside.

In contradiction to this, however, it was shown that stachyose required seven mols. of periodate for complete oxidation, three mols. of formic acid being liberated (Hérissey, Wickström, and Courtois, *Bull. Soc. Chim. biol.*, 1951, **33**, 642). Samples from three different sources (*Stachys tubifera*, *Plantago maritima*, and *Leucoema glauca*) gave identical results. The structure proposed above would require only six mols. of periodate, while two mols. of formic acid would be produced. The octaldehyde produced in the above reaction, on further oxidation with bromine water, gave a C_8 acid, hydrolysed to glyoxylic, glyceric, and hydroxypyruvic acids. A similar treatment of a compound containing a 1 : 4-linked glucose unit would give D-erythronic acid, but none could be identified. In support of these observations, Hérissey, Wickström, Courtois, and Le Dizet (Congr. Int. Biochim., 1952, Rés. des Comm., p. 311) found that no appreciable amounts of formaldehyde were liberated on periodate oxidation of manninotriose, in accordance with the presence of a 1 : 6-linked glucose unit. Further, manninotriose, on treatment with α-galactosidase for short periods, yielded a disaccharide with the same R_G value on the paper chromatogram as melibiose. These results can only be explained if we assume that, in stachyose, the glucose residue is linked through $C_{(1)}$ and $C_{(6)}$, and hydrolysis of methylated stachyose should, therefore, yield 2 : 3 : 4-trimethyl D-glucose.

In the present investigation soya-bean was used as a source of stachyose. The product, purified by chromatography, showed $[\alpha]_D^{17}$ +102° in water and on hydrolysis yielded galactose (2 mols.), glucose (1 mol.), and fructose (1 mol.). Oxidation with potassium metaperiodate (Halsall, Hirst, and Jones, *J.*, 1947, 1427) in the dark gave formic acid (2·33 mols.). This figure is somewhat lower than that obtained by Hérissey *et al.* (*loc. cit.*); it was found, however, that after prolonged oxidation, the amounts of formic acid produced began to drop, presumably owing to its oxidation. It is thus reasonable to assume that the final value would be higher. Oxidation of stachyose with sodium metaperiodate indicated an uptake of *ca.* 7 mols., and no formaldehyde could be detected.

Stachyose was methylated, first with methyl sulphate and sodium hydroxide, then with the Purdie reagents, to yield a product which showed OMe 48·0%, and $[\alpha]_D^{19}$ +130° in $CHCl_3$ (cf. $[\alpha]_D^{24\cdot5}$ +133·6° in C_6H_6; Onuki, *loc. cit.*). This was hydrolysed and the mixture

of methylated sugars separated by partition on a column of cellulose (Hough, Jones, and Wadman, *J.*, 1949, 2511) into four fractions.

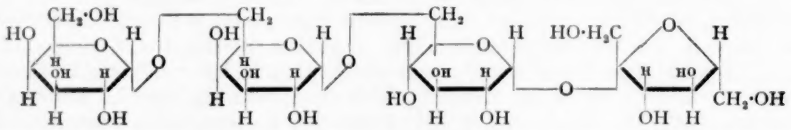
Fraction I (24%; based on weight recovered from the column) gave a spot on the paper chromatogram of the same R_G value as tetramethyl fructofuranose, as well as a small amount of, probably, tetramethyl glucopyranose. Tetramethyl D-fructofuranose was identified by the formation of the crystalline tetramethyl D-fructofuranamide (Avery, Haworth, and Hirst, *J.*, 1927, 2313).

Fraction II (58%) gave spots on the chromatogram corresponding to tetramethyl galactopyranose, 2 : 3 : 4-trimethyl glucose, and a small amount of 2 : 3 : 4-trimethyl galactose. On treatment with methanolic hydrogen chloride, it yielded mixed methylglycosides which after fractionation by solvent extraction (Brown and Jones, *J.*, 1947, 1344) gave syrups (*a*) and (*b*). Hydrolysed (*a*) contained 2 : 3 : 4 : 6-tetramethyl galactose, identified as the aniline derivative, and 2 : 3 : 4-trimethyl glucose; hydrolysed (*b*) contained 2 : 3 : 4-trimethyl glucose and 2 : 3 : 4-trimethyl galactose.

Fraction III (7%) was found by paper chromatography to be a mixture of trimethyl glucose and trimethyl galactose. This was combined with (*b*) and the sugars were separated on a column of cellulose into approximately equal amounts of 2 : 3 : 4-trimethyl D-glucose and 2 : 3 : 4-trimethyl D-galactose. The syrupy glucose derivative (OMe, 41·0%), $[\alpha]_D^{18}$ +60·5°, with periodate (Bell, *J.*, 1948, 992) gave formaldehyde (27% of theory), and authentic 2 : 3 : 4-trimethyl D-glucose gave a 35% yield. Demethylation (Hough, Jones, and Wadman, *J.*, 1950, 1702) afforded only glucose. Methylglycoside formation, both at room temperature and at 75°, followed similar routes {$[\alpha]_D^{18}$ +60° ⟶ −18°; values quoted for 2 : 3 : 4-trimethyl D-glucose are: free sugar, +60°; β-methylglycoside, −21° (Peat, Schluchterer, and Stacey, *J.*, 1939, 581)}. Treatment of the syrup with aniline in ethanol gave crystalline 2 : 3 : 4-trimethyl *N*-phenyl-D-glucosylamine. Examination of the free sugar on the chromatogram confirmed the presence of 2 : 3 : 4-trimethyl D-glucose. No 2 : 3 : 6-trimethyl glucose could be detected.

Fraction IV (11%) crystallised and was fully identified as 2 : 3 : 4-trimethyl D-galactose.

Thus, hydrolysis of methylated stachyose yielded tetramethyl D-fructofuranose, tetramethyl D-galactopyranose, 2 : 3 : 4-trimethyl D-glucose, and 2 : 3 : 4-trimethyl D-galactose in approximately equimolecular proportions. This result is in agreement with the views of Hérissey *et al.* (*loc. cit.*), and stachyose is represented by the annexed formula.



Experimental

Evaporations were conducted under diminished pressure. Temperatures recorded are bath-temperatures. Fractions from the cellulose column were evaporated to dryness, dissolved in water, digested with charcoal, and filtered hot; the aqueous solution was then evaporated to dryness and exhaustively extracted with boiling acetone, and the extracts were evaporated to dryness.

Extraction of Stachyose.—Soya-bean meal (250 g.) was ground in a hand mortar and extracted with boiling aqueous ethanol (70%; 1 l.) with continuous stirring for 6 hours. After filtration the residue was re-treated as above and the extracts were combined. The precipitate which settled out on cooling was removed by filtration, and the filtrate evaporated to a syrup. This procedure was repeated with three further 250-g. portions of meal, and the syrups were combined and dissolved in water (1 l.). The solution was heated to 95°, cadmium sulphate (10%; 100 c.c.) and sodium hydroxide (0·5N; 50 c.c.) were added, and the mixture was kept at 95° for a further 3 minutes. After cooling to room temperature and filtration, de-ionisation with Amberlite resins (I.R.-100 and IR-4B) yielded a solution from which the last traces of protein were removed by shaking with chloroform and butanol (Sevag, Lackmann, and Smollens, *J. Biol. Chem.*, 1938, **124**, 425). The product was warmed with a small amount of charcoal and filtered.

The volume of the extract was reduced to *ca.* 100 c.c. and added slowly with continuous stirring to ethanol (900 c.c.), to yield a brown gummy precipitate. This was separated on the

centrifuge, washed with absolute ethanol, and dried in a vacuum-desiccator ($CaCl_2$). This material showed $[\alpha]_D^{17}$ +67° (*c*, 0·9 in H_2O). Examination on the paper chromatogram indicated the presence of sucrose, a trisaccharide, and stachyose. After several reprecipitations from 90% ethanol the product showed $[\alpha]_D^{19}$ +85° in H_2O.

Preparation and Use of the Charcoal Column (cf. Whistler and Durso, *J. Amer. Chem. Soc.*, 1950, **72**, 677).—Decolourising charcoal (May and Baker; 50 g.) and "Hyflo Supercel" (50 g.), made into a paste with water, were poured into a column. The mixture was allowed to drain till the liquid level was *ca.* 1—2 cm. from the top of the column, which was never allowed to run dry, and then washed with water (1 l.).

The oligosaccharide mixture, in water (200 c.c.), was passed through the column. The sucrose and most of the trisaccharide which remained on the column were removed by elution with 5% aqueous ethanol. The tetrasaccharide contaminated with a little trisaccharide was recovered from the column by elution with 20% aqueous ethanol, and the eluate evaporated to dryness, dissolved in water, and purified as before on a second column. The final solution was evaporated to dryness and dissolved in water (230 c.c.), and the stachyose was precipitated by the addition of ethanol (2 l.). The product was a white powder (6·0 g.). A further crop of stachyose (0·8 g.) was obtained by concentrating the mother-liquors from the above precipitation and adding an excess of ethanol. The precipitates were combined, dissolved in water, and reprecipitated in 95% ethanol. This gave pure stachyose (6·5 g.), $[\alpha]_D^{17}$ +102° (*c*, 1·6 in H_2O). On examination by means of the paper chromatogram, with butanol–pyridine–water–benzene (5 : 3 : 3 : 1) as solvent (de Whalley, Albon, and Gross, *Analyst*, 1951, **76**, 287), only one spot was obtained (travelled 1 cm.; sucrose on same paper travelled 15·6 cm.). With amyl alcohol–pyridine–water (7 : 7 : 6) (Jeanes, Wise, and Dimler, *Analyt. Chem.*, 1951, **23**, 415) a single spot was again obtained (10·7 cm. from starting line). A test for the sucrose linkage with diazouracil (Raybin, *loc. cit.*) gave a positive result.

Hydrolysis.—Stachyose (*ca.* 10 mg.) was heated with sulphuric acid (3%; 4 c.c.) in a sealed tube at 100° for 6 hours. After neutralisation and filtration, the filtrate was evaporated to dryness and the sugars were estimated by paper chromatography (Nelson, *J. Biol. Chem.*, 1944, **153**, 375; Laidlaw and Reid, *J. Sci. Food Agric.*, 1952, **3**, 19) (Found, in two concordant analyses: galactose, 0·19 mg.; glucose, 0·09 mg.; fructose, 0·09 mg.).

Periodate Oxidation.—Stachyose (0·1 g.) was dissolved in aqueous sodium metaperiodate (0·2M; 10 c.c.). The periodate uptake, determined by the arsenite method, was 5·81 (2 hr.), 6·33 (21 hr.), 6·67 (44 hr.), 7·28 (5 days), expressed as moles of sodium periodate consumed per mole of stachyose.

Oxidation with potassium periodate (*loc. cit.*) gave the following results (expressed as moles of formic acid liberated per mole of stachyose): 0·95 (1 day); 1·97 (4 days); 2·09 (6 days); 2·34 (11 days). With a higher concentration of stachyose the values obtained were 0·86 (21 hours); 2·31 (4 days). In a third trial stachyose (0·1338 g.) was dissolved in water (20 c.c.), and sodium metaperiodate (0·075M; 30 c.c.) was added. The formic acid produced was 1·33 (1·25 hr.), 1·68 (4 hr.), 2·21 (1 day), 2·33 (2 days). In each case the titre fell slightly on prolonged storage.

The solution from the third trial above (3 c.c.), after 3 days at room temperature, was treated with the dimedon reagent (Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1475). No formaldehyde–dimedon compound was produced.

Methylation.—Stachyose (4·5 g.) was dissolved in water (50 c.c.), and sodium hydroxide (30%; 50 c.c.) added. Methyl sulphate (100 c.c.) and sodium hydroxide (30%; 200 c.c.) were run in during 4 hours at room temperature with continuous stirring. The solution was then set aside overnight. Solid sodium hydroxide (40 g.) was added and methyl sulphate (70 c.c.) run in during 4 hours. The solution was again left overnight. Water (500 c.c.) was added and the solution was extracted with chloroform (4 × 500 c.c.). The extracts were combined, washed twice with water, dried (Na_2SO_4), and evaporated to a clear syrup (2·8 g.). To the residual sodium hydroxide solution was added solid sodium hydroxide (50 g.), and methyl sulphate (100 c.c.) was run in during 6 hours. Extraction of the product and treatment as above yielded a further 0·7 g. of methylated material. The combined syrups were methylated in chloroform (50 c.c.) with silver oxide and methyl iodide at 45°. After three further such methylations the product was dissolved in water, and the solution heated with charcoal, filtered, and evaporated to dryness. The residue was extracted with acetone and the extracts were evaporated to yield a non-reducing syrup (2·68 g.), n_D^{20} 1·4692 (Found: OMe, 48·0. Calc. for $C_{38}H_{70}O_{21}$: OMe, 50·3%). A further methylation with methyl iodide did not increase the methoxyl content. The product showed $[\alpha]_D^{19}$ +130° (*c*, 1·07 in $CHCl_3$).

Hydrolysis and Fractionation.—The syrup (2·43 g.) was heated with sulphuric acid (2% w/v; 70 c.c.) at 100°. $[\alpha]_D^{18}$ were +132° (1 hr.), +129° (2 hr.), +122° (4 hr.), +116° (6 hr.). Concentrated sulphuric acid (2·3 c.c.) was added (total acid concentration 8%) and hydrolysis was continued {$[\alpha]_D^{18}$ +115° ($\frac{3}{4}$ hr.), +113° (2 hr.), +110° (3 hr.), +109° (4 hr., const.). The solution was neutralised with calcium carbonate, filtered, and evaporated to dryness. Extraction of the residue with boiling acetone and evaporation of the extracts yielded a syrup which was fractionated on a column of cellulose (20″ × 1·3″) (*loc. cit.*), with butanol–light petroleum (b. p. 100—120°) (1 : 2) saturated with water as solvent, giving fractions: I, 0·45 g.; II, 1·10 g.; III, 0·14 g.; IV, 0·21 g.

Fraction I contained tetramethyl fructofuranose and a very small amount of tetramethyl glucose and showed $[\alpha]_D^{18}$ +29° (*c*, 1·32 in H_2O). The syrup (0·2 g.) was oxidised with nitric acid (Avery, Haworth, and Hirst, *loc. cit.*). Esterification, methylation, and distillation of the product gave a non-reducing syrup (0·1 g.) which on treatment with methanolic ammonia yielded tetramethyl fructofuranamide. After recrystallisation from light petroleum containing 2% of ethyl acetate, this showed m. p. 100°, not depressed on admixture with an authentic specimen.

Investigation of fraction II on the paper chromatogram indicated it to be a mixture of tetramethyl galactose, 2 : 3 : 4-trimethyl glucose, and a smaller amount of 2 : 3 : 4-trimethyl galactose. The syrup (1·05 g.) was heated in methanolic hydrogen chloride (2%; 100 c.c.) under reflux: $[\alpha]_D^{18}$ were +79° (zero time), +98° (2 hr., const.). The solution was neutralised with silver carbonate, filtered, and evaporated, to yield a non-reducing syrup which was dissolved in water (50 c.c.). This solution was extracted continuously with light petroleum (b. p. 40—60°) (Brown and Jones, *loc. cit.*) to yield fractions: (i) 3·75 hr., 0·20 g., n_D^{18} 1·4509, (ii) +4 hr., 0·10 g., n_D^{20} 1·4512; (iii) +11 hr., 0·10 g., n_D^{20} 1·4510; (iv) +8 hr., 0·08 g., n_D^{20} 1·4510. These were combined to give (*a*) 0·48 g. A further fraction (*b*) 0·49 g., n_D^{20} 1·4570, was obtained by evaporation of the aqueous solution.

Syrup (*a*) (0·45 g.) was hydrolysed with sulphuric acid (2%; 25 c.c.) at 100°. $[\alpha]_D^{18}$ were +102° (zero time), +107° (2 hr.), +106° (4 hr., const.). The reducing syrup (0·41 g.) obtained was treated with aniline in ethanol. This gave tetramethyl *N*-phenyl-D-galactopyranosylamine, m. p. 195°, not depressed on admixture with an authentic specimen, and some syrupy material. The residual syrup was heated at 100° with sulphuric acid (2%; 25 c.c.) for 1 hour, then neutralised with barium carbonate, the solution extracted several times with ether, and the aqueous solution evaporated to yield a syrup (0·15 g.). Examination of this product on the paper chromatogram, with benzene (167)–ethanol (47)–water (16) as solvent, indicated it to be mainly composed of 2 : 3 : 4-trimethyl glucose with a small amount of 2 : 3 : 4-trimethyl galactose.

Syrup (*b*) was heated in sulphuric acid (2%; 30 c.c.) at 100°. $[\alpha]_D^{18}$ were +140° (zero time), +131° (6 hr.). The syrup was recovered from the solution in the usual manner and subjected to further hydrolysis with nitric acid (2%; 50 c.c.) at 100°. $[\alpha]_D^{18}$ were +106° (zero time), +98° (3 hr.), +96° (5 hr., const.). Examination of the product on the paper chromatogram as above indicated the presence of 2 : 3 : 4-trimethyl glucose and 2 : 3 : 4-trimethylgalactose. No tetramethyl galactose could be detected.

Fraction III was combined with hydrolysed (*b*) and fractionated on a column of cellulose to give 2 : 3 : 4-trimethyl D-glucose (0·23 g.) and 2 : 3 : 4-trimethyl D-galactose (0·25 g.).

Identification of 2 : 3 : 4-*trimethyl* D-*glucose*. The syrup showed $[\alpha]_D^{18}$ +60·5° (*c*, 0·8 in H_2O) and had OMe, 41·0 (Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

The syrup (8 mg.) with hydrobromic acid (48%) (Hough, Jones, and Wadman, *loc. cit.*) gave glucose, identified on the paper chromatogram.

The syrup (8·43 mg.) on oxidation with periodate (Bell, *loc. cit.*) yielded formaldehyde, identified as the dimedon compound (3·96 mg., 27% of theory), m. p. and mixed m. p. 188—190°. Authentic 2 : 3 : 4-trimethyl D-glucose (10·6 mg.) gave the dimedon compound (6·56 mg., 35%).

The syrup (0·0215 g.) was dissolved in methanolic hydrogen chloride (1%; 5 c.c.). The rotational changes of the solution at room temperature and at 75° were observed: at room temp., $[\alpha]_D^{18}$ +53·5° (5 min.), +46° (35 min.), +40° (50 min.), +30° (2 hr.), +14° (4 hr.), −16° (22 hr., const.); at 75°, $[\alpha]_D^{18}$ +23° (45 min.), +7° (1½ hr.), −12° (3½ hr.), −18° (4½ hr., const.).

The syrup (0·1 g.) with aniline in ethanol yielded 2 : 3 : 4-trimethyl *N*-phenyl-D-glucosylamine, m. p. 140°. On examination on the paper chromatogram with amyl alcohol (4)–acetic acid (1)–water (5), one spot only was obtained, having R_G 0·79 corresponding to authentic 2 : 3 : 4-trimethyl glucose. 2 : 3 : 6-Trimethyl D-glucose, run on the same paper, had R_G 0·74. Similar results were obtained with benzene–ethanol–water as solvent.

Fraction IV crystallised as the monohydrate (cf. McCreath and Smith, *J.*, 1939, 387). After

being washed with light petroleum (b. p. 40—60°) it showed m. p. 75°. When dried in a vacuum-desiccator (P_2O_5), the crystals tended to become syrupy. Prolonged trituration with ethyl acetate–light petroleum gave a product with m. p. 83° (previous softening). The crystals showed $[\alpha]_D^{18}$ +135° (15 min.) ⟶ +114·5° (3 hr., const.) (*c*, 0·3 in H_2O).

Demethylation with hydrogen bromide (*loc. cit.*) gave galactose only.

Oxidation with periodate (Bell, *loc. cit.*) gave formaldehyde, identified as the dimedon compound. Treatment of fraction IV with aniline in ethanol gave 2 : 3 : 4-trimethyl *N*-phenyl-D-galactosylamine, m. p. 165—167°, unchanged on admixture with an authentic specimen.

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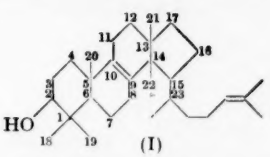
115. *Triterpenoids. Part IX.* The Constitution of Lanostadienol (Lanosterol).*

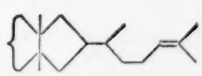
By C. S. BARNES, D. H. R. BARTON, A. R. H. COLE, J. S. FAWCETT, and B. R. THOMAS.

Reduction of 8 : 11-diketolanostan-2-yl acetate with sodium and propanol affords lanostane-2β : 8β : 11α-triol, which is easily acylated to the tribenzoate and to the triacetate. Vigorous chromic acid oxidation of the latter affords (*a*) 2β : 8β : 11α-triacetoxytrisnorlanostanoic acid, the constitution of which was confirmed by partial synthesis (of the methyl ester) from 2β-hydroxy-8 : 11-diketotrisnorlanostanoic acid, (*b*) 2β : 8β : 11α-triacetoxy-23-hydroxytrisnorlanostanoic acid [27→23]-lactone, and (*c*) 2β : 8β : 11α-triacetoxylanan-17-one. The characterisation of the grouping >CMe·CO·$[CH_2]_2$·CMe< in a five-membered ring in this ketone by both chemical and physical methods excludes the possible attachment of the lanosterol side chain at $C_{(16)}$ and confirms the size of ring D.

THE present paper describes work designed to confirm the correctness of the isoprenoid formulæ (I) and (II) for lanostadienol (Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142; Barton, Fawcett, and Thomas, *ibid.*, p. 3147; Ruzicka *et al.*, *Helv. Chim. Acta*, 1951, **34**, 1585; 1952, **35**, 66, 503; Barton, McGhie, *et al.*, *Chem. and Ind.*, 1951, 1067), with the added objective of distinguishing between them. A preliminary account of this work (Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426) has already been published.



(I)



(II)

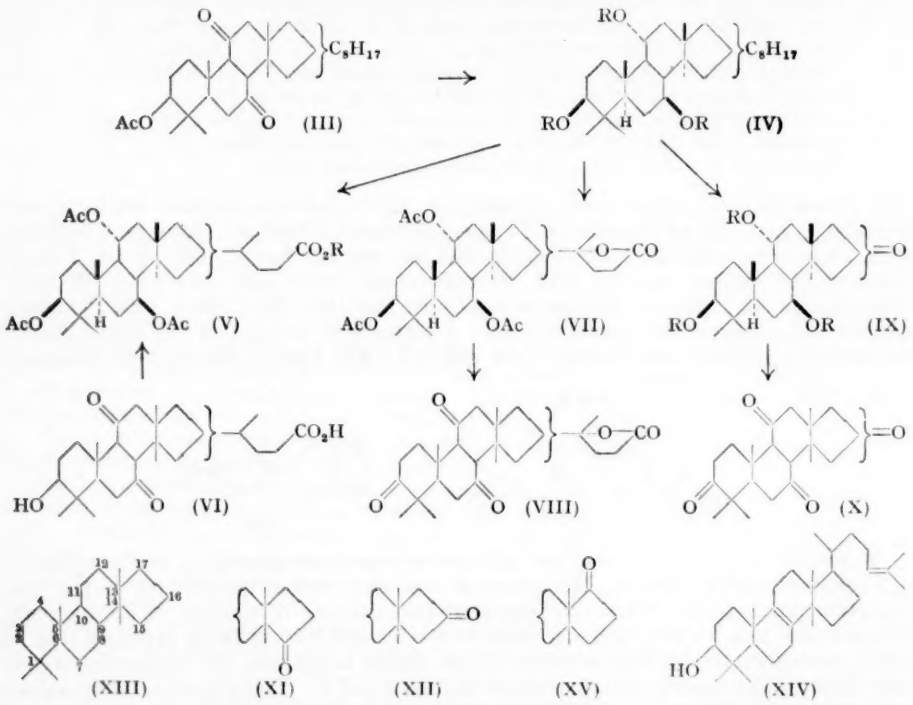
It seemed to us *a priori* that the isolation of 6-methylheptan-2-one in the oxidation of lanostenyl acetate (Barton, McGhie, *et al.*, *loc. cit.*) implied the presence in the total oxidation products of a tetracyclic fragment characteristic of the rest of the molecule. However a search for this fragment proved abortive and it accordingly appeared that, in order to secure a higher concentration of the desired compound, the tetracyclic nucleus must be stabilised against oxidative attack in rings B and C. This was achieved by sodium and propanol reduction of 8 : 11-diketolanostanyl acetate (III) (Dorée, McGhie, and Kurzer, *J.*, 1948, 988) to lanostane-2β : 8β : 11α-triol † (IV; R = H), characterised as the

* Part VIII, *J.*, 1952, 3751.

† The stereochemistry of this and other lanostadienol derivatives is discussed in the following paper.

triacetate and the tribenzoate. The tri-equatorial character, and hence ease of acylation, of this triol was predicted from its mode of preparation (cf. Barton, *Experientia*, 1950, **6**, 316; Barton and Rosenfelder, *J.*, 1951, 1048). 2β : 8β : 11α-Triacetoxylanostane (IV; R = Ac) proved suitable for vigorous chromic acid oxidation to the desired tetracyclic fragment.

After oxidation of the triacetate in acetic acid–aqueous sulphuric acid at 26—30° for 14 hours the product was separated into acid and neutral fractions. The acid fraction on methylation and chromatography afforded methyl 2β : 8β : 11α-triacetoxytrisnorlanostanoate (V; R = Me), the constitution of which was confirmed by its preparation by reduction of 2β-hydroxy-8 : 11-diketotrisnorlanostanoic acid (VI) (McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165; Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 497) with sodium and propanol followed by acetylation and methylation. The neutral fraction, on chromatography, furnished two crystalline substances. One of these was a high-melting compound, $C_{33}H_{50}O_8$, which was shown by its infra-red spectrum (band at 1780 cm.$^{-1}$ in CS_2) to be a γ-lactone. Like the corresponding lactone obtained in the cholesteryl acetate dibromide oxidation (see Ryer and Gebert, *J. Amer. Chem. Soc.*, 1952, **74**, 4336; cf. Billeter and Miescher, *Helv. Chim. Acta*, 1949, **32**, 564) the lactone ring of the lanostane derivative must be closed on to the tertiary carbon one removed from the ring carbon atom to which the side chain is attached, and therefore we formulate it as (VII). There was some difficulty in obtaining consistent analyses for the triacetate lactone itself; in consequence it was hydrolysed to the corresponding tetrahydroxy-acid (which at once relactonised) and then converted by chromic acid oxidation into the corresponding triketo-lactone (VIII). The other neutral compound had the composition



$C_{28}H_{42}O_7$ and was shown to be a ketone by the ultra-violet spectrum ($\lambda_{max.}$ 293 mμ; ε, 33) and by the infra-red spectrum (see further below). This ketone is formulated as (IX; R = Ac). Because of the acetate residues the band in the infra-red spectrum

near 1740 cm.$^{-1}$ due to the ketone grouping in a five-membered ring was masked. Alkaline hydrolysis gave the corresponding trihydroxy-ketone (IX; R = H), which gave a tribenzoate (IX; R = Bz). The latter showed the benzoate carbonyl band in the infra-red at 1718 cm.$^{-1}$ and also the expected ketone band at 1747 cm.$^{-1}$. The triacetoxy-ketone (IX; R = Ac) was further characterised by conversion into its oxime acetate, and by hydrolysis and oxidation to the tetraketone (X).

On the basis of the two isoprenoid formulæ (I) and (II) (IX; R = Ac) would be represented by the partial formulæ (XI) and (XII) respectively. The former contains the grouping >CMe·CO·[CH_2]$_2$·CMe< (*A*) and the latter the grouping >CMe·CH_2·CO·CH_2·CMe< (*B*). Decisive evidence in favour of (*A*) was obtained as follows.

(i) The ketone group in (*B*) should not be subject to significant steric hindrance, since it is flanked by two CH_2 groups. In contrast the triacetoxy-ketone (IX; R = Ac) afforded a 2 : 4-dinitrophenylhydrazone with difficulty and only under reflux, the rate of reaction corresponding approximately to that of an 8-keto-group in the lanostane series (Barton, Fawcett, and Thomas, *loc. cit.*). As would be expected, 6- and 7-ketocholestanyl acetate, cholestan-3- and -4-one, 17-ketoandrostan-3β-yl acetate, and A-norcholestanone gave 2 : 4-dinitrophenylhydrazones rapidly under similar conditions but at room temperature.

(ii) In quantitative bromination experiments (see Experimental) the results shown in Table 1 were obtained. Clearly the ketone (IX; R = Ac) contains only two α-hydrogen atoms replaceable by bromine. These results were confirmed by the isolation of 2β : 8β : 11α-triacetoxydibromolananone * after complete bromination of (IX; R = Ac). As would be expected this dibromo-ketone did not consume any more bromine even under vigorous brominating conditions. The 2β : 8β : 11α-triacetoxylananone must therefore contain the grouping (*A*) and not (*B*).

TABLE 1.

Compound	Uptake of Br, mols. 1 day	2 days	3 days	4 days
17-Ketoandrostan-3β-yl acetate	2·0	2·1	2·2	2·2
A-Norcholestanone	2·75	3·0	3·2	3·25
2β : 8β : 11α-Triacetoxylananone (IX; R = Ac)	1·6	1·9	2·1	2·1

(iii) It has recently been shown by R. N. Jones, Cole, *et al.* (*J. Amer. Chem. Soc.*, 1952, **74**, 5648, 5662) that ketones with CH_2 adjacent to the carbonyl group in a five-membered ring have a characteristic absorption maximum near 1410 cm.$^{-1}$ in the infra-red and, since this band is due to a bending vibration of the $-CH_2-$, its intensity (Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80) should be proportional to the number of flanking methylene groups. Table 2 shows the application of this principle to various of the compounds described in the present paper. It will be seen that, as would be expected, only A-norcholestanone shows an intensity of absorption corresponding to two α-CH_2 groups. The derivatives of (IX; R = H) must therefore contain the grouping (*A*) and not (*B*).

TABLE 2.

Compound	Infra-red band frequency, cm.$^{-1}$	Apparent integrated absorption intensity,* *I*	No. of α-CH_2 groups, *n*	*I*/*n*
17-Ketoandrostan-3β-yl benzoate	1408	280	1	280
17-Ketoandrostan-3β-yl acetate	1407	320	1	320
A-Norcholestanone	1410	620	2	310
2β : 8β : 11α-Triacetoxylananone (IX; R = Ac)	1412	280	1	280
2β : 8β : 11α-Tribenzoyloxylananone (IX; R = Bz)	1411	300	1	300

* After graphical separation of overlapping bands.

With these results and with the assumed applicability of the isoprene rule, formula (XI) (2β : 8β : 11α-triacetoxylanan-15-one) can be deduced for the triacetoxy-ketone and the corresponding formula (I) for lanosterol. Ruzicka, Jeger, and their collaborators have

* We propose that the annexed tetracyclic nucleus (XIII), which is a trimethylandrostane, should be given the trivial name lanane and numbered as indicated.

however always been careful to point out that, if the isoprene rule is *not* applicable to the skeleton of lanosterol, then the side chain may also be attached at $C_{(17)}$. Curtis, Fridrichsons, and Mathieson (*Nature*, 1952, **170**, 321) have recently reported on the *X*-ray diffraction analysis of lanostenyl iodoacetate from which they conclude that the side chain is indeed attached at $C_{(17)}$, so that lanostadienol has the formula (XIV). There is, of course, nothing in the results described here which excludes formula (XIV), for the derived ketone (XV) would also contain the grouping (*A*). On the assumption that chemical verification of the attachment of the side chain at $C_{(17)}$ will eventually be forthcoming,* we accept the *X*-ray evidence. In our opinion, the latter represents an important contribution to the chemistry, and especially to the stereochemistry (see the following paper), of lanostadienol.

Experimental

M. p.s are uncorrected. Rotations were determined in chloroform solution at room temperature, which varied from 15° to 25°. Values of $[\alpha]_D$ have been approximated to the nearest degree. Light petroleum refers to the fraction of b. p. 40—60°.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanolic, ethanolic, or dioxan–methanolic solution, depending on the solubility requirements of the ester.

Ultra-violet absorption spectra were measured in ethanol solution with a Unicam S.P. 500 Spectrophotometer. Infra-red spectra were measured in carbon tetrachloride with a Perkin–Elmer Model 12 C Spectrometer (sodium chloride prism). We gratefully acknowledge permission to use the instrument at the Chester Beatty Institute for this purpose.

Lanostane-2β : 8β : 11α-*triol* (IV; R = H) *and its Derivatives*.—Sodium (20 g.) was added portionwise to a refluxing solution of 8 : 11-diketolanostanyl acetate (20 g.) in propanol (200 ml.) during 2 hours. Decomposition of the excess of sodium by aqueous ethanol, followed by isolation of the product in the usual manner, gave *lanostane*-2β : 8β : 11α-*triol*. Recrystallised from aqueous propanol this had m. p. 207—208°, $[\alpha]_D$ +3° (*c*, 1·10) (Found : C, 76·95; H, 11·7. $C_{30}H_{54}O_3,0{\cdot}5H_2O$ requires C, 76·4; H, 11·75%).

With pyridine–acetic anhydride on the steam-bath (30 min.) the triol yielded the corresponding *triacetate*, m. p. 156° (from methanol), $[\alpha]_D$ +29° (*c*, 2·18) (Found : C, 73·9; H, 10·35. $C_{36}H_{60}O_6$ requires C, 73·4; H, 10·3%). Benzoyl chloride similarly gave the *tribenzoate*, m. p. 162—164° (from chloroform–methanol), $[\alpha]_D$ +46° (*c*, 1·77), $\lambda_{max.}$ 231, 274, and 281 mμ (ε 42,000, 2800, and 2300 respectively) (Found : C, 74·4; H, 8·3; Cl, 6·8. $C_{51}H_{66}O_6,0{\cdot}5CHCl_3$ requires C, 74·1; H, 8·05; Cl, 6·4%).

Chromic Acid Oxidation of 2β : 8β : 11α-*Triacetoxylanostane* (IV; R = Ac).—Chromium trioxide (40 g.) in water (40 ml.), acetic acid (200 ml.), and concentrated sulphuric acid (20 ml.) was added during 45 minutes to a stirred solution of 2β : 8β : 11α-triacetoxylanostane (20 g.) in acetic acid (400 ml.) and acetic anhydride (20 ml.), kept throughout at 26—30°. The mixture was then stirred overnight at room temperature, poured into water (4 l.), and extracted with ether. The ethereal extract was separated into acid (9·8 g.) and neutral (6·0 g.) fractions.

The acid moiety was methylated with diazomethane and chromatographed over alumina (Peter Spence, grade H), to give as the only crystalline fractions (eluted with 2 : 1 benzene–ether) *methyl* 2β : 8β : 11α-*triacetoxytrisnorlanostanoate* (V; R = Me) (1·9 g.), m. p. 195—196° (from ethyl acetate–light petroleum), $[\alpha]_D$ +25° (*c*, 1·19) (Found : C, 68·75; H, 9·55. $C_{34}H_{54}O_8$ requires C, 69·1; H, 9·2%). There was no depression in m. p. on admixture with an authentic specimen of the same m. p. prepared as described below.

The neutral fraction was chromatographed over alumina (Peter Spence, grade H) to give two crystalline products. (i) Elution with 4 : 1 benzene–ether afforded 2β : 8β : 11α-*triacetoxylanan*-17-*one* (IX; R = Ac) (750 mg.), m. p. 190—191° (from aqueous methanol), $[\alpha]_D$ +41° (*c*, 1·52), $[M]_D$ +201°, $\lambda_{max.}$ 293 mμ (ε, 33) (Found : C, 68·45; H, 8·6. $C_{28}H_{42}O_7$ requires C, 68·55; H, 8·6%). (ii) Elution with ether gave 2β : 8β : 11α-*triacetoxy*-23-*hydroxytrisnorlanostanoic acid* [27→23]-*lactone* (VII) (500 mg.), m. p. 272—274° (from methanol), $[\alpha]_D$ +37° (*c*, 1·47); it was sublimed for analysis (Found : C, 68·4; H, 8·6. $C_{33}H_{50}O_8$ requires C, 68·95; H, 8·75%).

Methyl 2β : 8β : 11α-*Triacetoxytrisnorlanostanoate* (V; R = Me) *from* 2β-*Hydroxy*-8 : 11-*diketotrisnorlanostanoic Acid* (VI).—The hydroxy-diketo-acid (1·0 g.) in refluxing propanol (50 ml.) was reduced by the addition of sodium until the solution was saturated. After being

* *Added, December 12th*, 1952.—Voser, Mijovic, Heusser, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1952, **35**, 2414) have now provided convincing *chemical* evidence for a $C_{(17)}$ side chain.

worked up in the usual way the trihydroxy-acid was acetylated with pyridine–acetic anhydride on the steam-bath for 1 hour and then methylated with diazomethane. Chromatography of the product over alumina and elution with 2 : 1 benzene–ether afforded methyl 2β : 8β : 11α-triacetoxytrisnorlanostanoate, m. p. 195—196°, $[\alpha]_D$ +23° (*c*, 1·76).

Derivatives of 2β : 8β : 11α-*Trihydroxylanan*-17-*one* (IX; R = H).—Alkaline hydrolysis of the triacetoxy-ketone afforded 2β : 8β : 11α-*trihydroxylanan*-17-*one*, m. p. 235—256° (from aqueous methanol) (Found: C, 71·45; H, 9·75. $C_{22}H_{36}O_4,0{\cdot}5CH_3{\cdot}OH$ requires C, 71·05; H, 10·05%). Repeated fractional crystallisation failed to alter the wide m. p. range.

2β : 8β : 11α-Trihydroxylanan-17-one with benzoyl chloride in pyridine on the steam-bath (30 min.) gave the *tribenzoate*, m. p. 172—175° (from chloroform–methanol), $[\alpha]_D$ +56° (*c*, 1·25), $\lambda_{max.}$ 231, 274, and 281 mμ (ε, 40,000, 2750, and 2200 respectively) (Found: C, 75·7; H, 7·2. $C_{43}H_{48}O_7$ requires C, 76·3; H, 7·15%).

2β : 8β : 11α-Triacetoxylanan-17-one (100 mg.) was treated with 2 : 4-dinitrophenylhydrazine (50 mg.) in refluxing ethanolic hydrochloric acid for 40 minutes. After the usual working up the product was re-acetylated with pyridine–acetic anhydride overnight at room temperature. Chromatography over alumina washed with ethyl acetate gave some unchanged triacetoxy-ketone and then the 2 : 4-*dinitrophenylhydrazone* (20 mg.). Recrystallised from chloroform–methanol this had m. p. 277—279°, $\lambda_{max.}$ 362 mμ (ε, 25,000) (Found: C, 60·55; H, 7·05; N, 8·4. $C_{34}H_{46}O_{10}N_4$ requires C, 60·85; H, 6·90; N, 8·35%).

2β : 8β : 11α-Triacetoxylanan-17-one (200 mg.) in pyridine was heated on the steam-bath for 1 hour with hydroxylamine hydrochloride. The derived oxime melted over a range (155—170°) which was not improved by crystallisation or careful chromatography. In the latter fractionation, however, the oxime behaved as a pure compound. Acetylation with pyridine–acetic anhydride overnight at room temperature gave the sharp-melting 2β : 8β : 11α-*triacetoxylanan*-17-*one oxime acetate*, m. p. 212—214° (from ethyl acetate–light petroleum), $[\alpha]_D$ +4° (*c*, 2·00) (Found: C, 65·6; H, 8·4; N, 2·65. $C_{50}H_{45}O_8N$ requires C, 65·8; H, 8·5; N, 2·55%).

2β : 8β : 11α-*Triacetoxy*-16 : 16-*dibromolanan*-17-*one and Bromination Experiments*.—2β : 8β : 11α-Triacetoxylanan-17-one (49 mg.), A-norcholestanone (Windaus and Uibrig, *Ber.*, 1914, **47**, 2384; Windaus and Dalmer, *ibid.*, 1919, **52**, 162) (39 mg.), and 3β-acetoxyandrostan-17-one (34 mg.) were each dissolved in "AnalaR" acetic acid (10 ml.), containing approx. 19 g. of bromine per 100 ml., with addition of hydrogen bromide [0·1 ml.; 50% (w/v) in acetic acid] and left at 40° in a thermostatically controlled oven. At suitable time intervals 1-ml. portions were removed and the bromine remaining (see Table 1) was determined in the usual way. A suitable control was also run.

The fully brominated lanane derivative, from an analogous experiment with 125 mg. of the ketone, was isolated in the usual way. Recrystallisation from aqueous methanol afforded 2β : 8β : 11α-*triacetoxy*-16 : 16-*dibromolanan*-17-*one*, m. p. 239—240°, $[\alpha]_D$ +43° (*c*, 0·74) (Found: Br, 24·8. $C_{28}H_{40}O_7Br_2$ requires Br, 24·7%). The dibromide was resistant to further bromination.

Lanane-2 : 8 : 11 : 17-*tetraone* (X).—2β : 8β : 11α-Trihydroxylanan-17-one (350 mg.) in "AnalaR" acetic acid (5 ml.) was treated with chromium trioxide (23 mg.) in a little aqueous "AnalaR" acetic acid and left overnight at room temperature. Isolation of the product in the usual way afforded *lanane*-2 : 8 : 11 : 17-*tetraone*, m. p. 293—295° (from chloroform–methanol), $[\alpha]_D$ +74° (*c*, 0·92), $[M]_D$ +265°, $\lambda_{max.}$ 292 mμ (ε, 133) (Found: C, 73·2; H, 8·15. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%).

2 : 8 : 11-*Triketo*-23-*hydroxytrisnorlanostanoic Acid* [27→23]-*Lactone* (VIII).—The corresponding triacetoxy-lactone (see above) (500 mg.) was hydrolysed by refluxing alcoholic potassium hydroxide (10%; 10 ml.) for 30 minutes, the solution evaporated to dryness under reduced pressure, and the residue dissolved in water. The clear solution was extracted repeatedly with ether, but there was no neutral fraction. The alkaline solution was acidified and extracted with ethyl acetate, and part of the extract acetylated with pyridine–acetic anhydride. Recrystallisation gave back the initial triacetoxy-lactone, identified by m. p. and mixed m. p. The remainder of the extract (2β : 8β : 11α-trihydroxy-lactone; 60 mg.) in acetic acid (2 ml.) was treated with chromium trioxide (50 mg.) and left overnight at room temperature. Isolation of the product in the usual way and crystallisation from chloroform–methanol furnished 2 : 8 : 11-*triketo*-23-*hydroxytrisnorlanostanoic acid* [27→23]-*lactone*, m. p. 280—283°, $[\alpha]_D$ +70° (*c*, 0·53) (Found: C, 73·2; H, 8·7. $C_{27}H_{38}O_5$ requires C, 73·25; H, 8·65%).

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BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, October 3rd,* 1952.]

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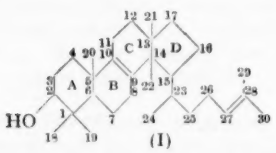
116. *Triterpenoids. Part X.* The Stereochemistry of Lanostadienol (Lanosterol).*

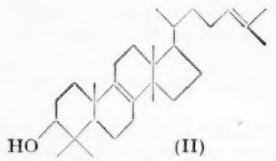
By C. S. BARNES, D. H. R. BARTON, J. S. FAWCETT, and B. R. THOMAS.

On the basis of molecular-rotation and conformational arguments configurations have been assigned to all the asymmetric centres in lanostanol and certain of its derivatives. The conclusions reached are in excellent agreement with those recently adduced by Curtis, Fridrichsons, and Mathieson (*Nature*, 1952, **170**, 321) on the basis of *X*-ray diffraction studies. A preliminary account of our views has already been published (Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426).

THE solution of the constitutional problem for lanostadienol (see preceding paper and references there cited) invites inquiry into the stereochemistry of the molecule. On the basis of conformational (Barton, *Experientia*, 1950, **6**, 316) and generalised molecular-rotation arguments (Klyne, *J.*, 1952, 2916; Stokes and Werner Bergmann, *J. Org. Chem.*, 1951, **16**, 1817; 1952, **17**, 1194) a purely chemical solution to the problem can be adumbrated. Two formulæ, (I) and (II), for lanostadienol are here considered. The first of these is the constitution of lanostadienol on the assumed applicability of the isoprene rule. The second non-isoprenoid formula is the only other solution to the problem which is possible on chemical evidence. That the latter is the correct solution has been argued by Curtis, Fridrichsons, and Mathieson (*loc. cit.*) on the basis of *X*-ray diffraction data.



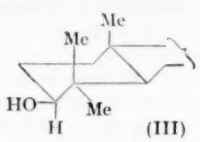
(I)



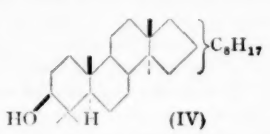
(II)

We commence by accepting the generalised molecular-rotation arguments of Klyne (*loc. cit.*) that rings A and B are *trans*-fused as in the other triterpenoids that have been investigated (see Barton and Holness, *J.*, 1952, 78). Since the angular methyl group at $C_{(5)}$ has the same configuration as the angular methyl group at $C_{(10)}$ in steroids (Klyne, *loc. cit.*) we envisage that it projects above the plane of the paper in the β-configuration.

The hydroxyl group at $C_{(2)}$ in lanostadienol is equatorial (cf. Barton, *loc. cit.*) as shown by its stability towards attempted epimerisation (Wieland, Pasedach, and Ballauf, *Annalen*,



(III)



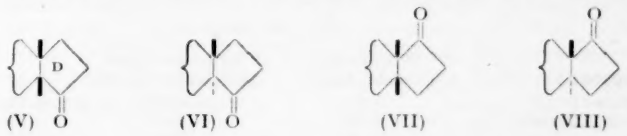
(IV)

1937, **529**, 68) and by its regeneration (in suitable derivatives) on reduction of the appropriate ketones with sodium and alcohol (*inter al.*, Marker, Wittle, and Mixon, *J. Amer.*

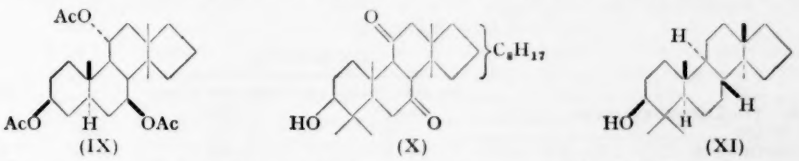
* Part IX, preceding paper.

Chem. Soc., 1937, **59**, 1368; Marker and Wittle, *ibid.*, p. 2289). It must therefore have the 2β-configuration as in (III), a conclusion which is confirmed (cf. Barton, *loc. cit.*; Barton and Holness, *loc. cit.*) by the well-established dehydration + rearrangement observed on treatment with phosphorus pentachloride (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467; Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818; Dorée, McGhie, and Kurzer, *Nature*, 1949, **163**, 140; *J.*, 1949, S 167). We have previously (Barton, Fawcett, and Thomas, *J.*, 1951, 3147) advanced arguments that the $C_{(13)}$ methyl group must be on the same side of the molecule as the $C_{(5)}$ methyl group; therefore the appropriate partial stereochemistry in (IV) may be deduced.

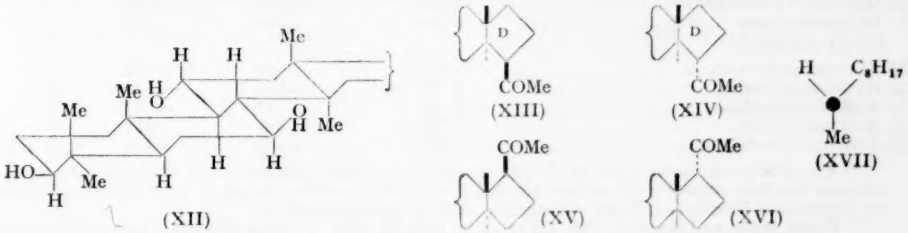
The stereochemistry of the $C_{(14)}$ methyl group can be established (Barnes, Barton, Cole, Fawcett, and Thomas, *loc. cit.*) by the generalised molecular rotation method. Four possibilities (V), (VI), (VII), and (VIII) have to be considered for ring D of the 2β : 8β : 11α-triacetoxylanan-15(or 17)-one described in the preceding paper. To differentiate between them the molecular-rotation contribution of the keto-group is required. This was determined by Wolff-Kishner reduction of the ketone, followed by reacetylation, to give



2β : 8β : 11α-triacetoxylanane (IX), which was further characterised by conversion into the corresponding triketone, lanane-2 : 8 : 11-trione. The difference in molecular rotation between the triacetoxylanane and the derived ketone was +110°, whilst that between the triketone and the corresponding tetraketone (see preceding paper) was +90°. The approximate molecular rotation contributions to be expected for structures (V) to (VIII) are (Klyne, *loc. cit.*) −500°, +250°, +500°, and +250° respectively. Clearly the experimental data exclude (V) as compared with (VI) and favour (VIII) relative to (VII).



It is now appropriate to discuss the ring fusion of compounds with rings B and C saturated. Such compounds are prepared *via* 2-hydroxylanostane-8 : 11-dione (X). We have shown (see Experimental section) that this diketone is stable to vigorous alkaline treatment and therefore both $C_{(9)}$ and $C_{(10)}$ must be in the more stable configuration. On the basis of conformational arguments (Barton, *loc. cit.*), especially those advanced by W. S. Johnson (*Experientia*, 1951, **7**, 315; cf. Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 2118; W. S. Johnson, *ibid.*, in the press) the configurations at $C_{(9)}$ and $C_{(10)}$ must be *trans* relative to each other



and *anti* relative to $C_{(14)}$ and $C_{(5)}$. We thus reach the stereochemical conclusions summarised for lanan-2-ol in (XI). Since sodium and alcohol reductions of ketone groups afford the thermodynamically more stable equatorial configurations (Barton, *loc. cit.*), the

stereochemistry of the lanostane-2 : 8 : 11-triol described in the preceding paper must be 2β : 8β : 11α- [see (XII)] in agreement with the ease of acylation (cf. Heusser, Anliker, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1537).

There remains for consideration the stereochemistry of the side chain. Of the four possible alternatives, (XIII)—(XVI), (XIII) is equivalent to (XVI), and (XIV) to (XV), on the basis of generalised molecular rotations. As Table 1 clearly shows, the molecular-rotation contribution of the side chain in appropriate methyl ketones, with respect to the corresponding *iso*octyl side chain compounds, corresponds closely to that for a 17β-acetyl group in the steroid series. On this count the lanostadienol side chain must be fused 15α based on (I) or 17β based on (II). This conclusion is also in agreement with the fact that the acetyl group and therefore, because of the method of synthesis, the side chain is fused to the ring system in the thermodynamically more stable configuration (McGhie and Pradhan, personal communication). On the basis of equatorial and polar bonds (with respect to ring C; see Barton, *loc. cit.*) this also means that the configuration must be 15α or 17β.

TABLE 1.

Compound	$[M]_D$ in $CHCl_3$: With *iso*octyl side chain	With side chain replaced by –COMe	Δ	Refs.
2-Hydroxylanostan-11-one	+275°	+410°	+135°	1, 2, 3
11-Ketolanostan-2-yl acetate	+291	+455	+164	1, 2, 3
Cholestanol	+ 89	+290	+201	4, 5
Cholestanyl acetate	+ 60	+277	+217	4, 5
17-*iso*Cholestanol	− 95	−248	−153	5, 6

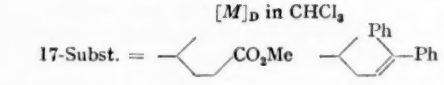
[1] Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893. [2] Voser, Jeger, and Ruzicka, *ibid.*, 1952, **35**, 503. [3] McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165; McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176. [4] Barton, *J.*, 1946, 1116. [5] Shoppee, *J.*, 1949, 1671. [6] $[M]_D$ for 17-*iso*cholestanol is assumed to be the same as that for 17-*isoallo*pregnane (Casanova and Reichstein, *Helv. Chim. Acta*, 1949, **32**, 647). The introduction of the 3β-hydroxyl group and the change from the saturated ethyl to the saturated *iso*octyl side chain can have but little effect on optical rotation (cf. Barton and Klyne, *Chem. and Ind.*, 1948, 755; Klyne, *loc. cit.*).

TABLE 2.

	$[M]_D$ in $CHCl_3$: No side chain	*iso*Octyl side chain	Δ	Refs.
2β : 8β : 11α-Triacetoxylanane	+81°	+170°	+89°	1
Androstane	+ 5	+ 91	+86	2
Androstan-3β-ol	+ 3	+ 89	+86	2, 3

[1] Exptl., this paper. [2] Barton and Klyne, *Chem. and Ind.*, 1948, 755. [3] Barton, *J.*, 1946, 1116.

TABLE 3.

Compound	$[M]_D$ in $CHCl_3$: 17-Subst. = 	Δ	Refs.
Lanane derivatives.			
2β-Hydroxy-11-ketolanane	+250°	+397°	+147°	1
8 : 11-Diketolanane	+266	+390	+124	2
Steroid derivatives.			
3β-Hydroxyandrost-5-ene	−198	− 74	+124	3, 4
3β-Hydroxyandrostane	+ 74	+204	+130	3, 5
3β-Acetoxyandrostane	+ 48	+183	+135	3, 5
3α-Acetoxytestane	+186	+345	+159	3, 5
3β-Acetoxy-11-ketotestane	+319 *	+458	+139	6, 7, 8, 9

* The literature values (refs. 6, 7, and 8) are for acetone solution. The calculated molecular rotation has been corrected for chloroform solution by the correction factor of +20° found applicable by Barton and Brooks (ref. 3) for various bile acid 12-keto-derivatives.

[1] Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 503. [2] Voser, Mijovic, Jeger, and Ruzicka, *ibid.*, 1951, **34**, 1585. [3] Barton and Brooks, *J.*, 1949, 2596. [4] Meystre, Wettstein, and Miescher, *Helv. Chim. Acta*, 1947, **30**, 1022. [5] Meystre and Miescher, *ibid.*, 1946, **29**, 33. [6] Lardon and Reichstein, *ibid.*, 1943, **26**, 586. [7] Hicks and Wallis, *J. Biol. Chem.*, 1946, **162**, 641. [8] Wintersteiner and Moore, *ibid.*, p. 725. [9] Wettstein and Meystre, *Helv. Chim. Acta*, 1947, **30**, 1262.

A further interesting aspect of the molecular-rotation properties of the lanostane side chain is brought out in Table 2. Again there is excellent agreement for a 15α- or 17β-fused side chain.

The remaining centre of asymmetry in the lanostadienol molecule is that at $C_{(23)}$. The configuration at this centre can be derived from molecular-rotation considerations. The change from the weak chromophore of a $C_{(26)}$-carbomethoxy-group to the corresponding strongly chromophoric diphenylethylene derivative (see Table 3) is attended by a change in molecular rotation of about +140 units. This molecular-rotation difference may be regarded as determined in the main part by the configuration at $C_{(23)}$. As shown in Table 3 exactly the same molecular-rotation difference is observed in the steroid series, where the corresponding centre of asymmetry at $C_{(20)}$ is of defined orientation (Wieland and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1922). We conclude that $C_{(23)}$ in lanostane compounds has the configuration indicated in (XVII). The latter depicts the view looking down the bond from the tetracyclic nucleus towards $C_{(23)}$. The conclusion reached is, of course, independent of the attachment of the side chain to $C_{(15)}$ or $C_{(17)}$.

It is instructive to compare the stereochemical conclusions in the present paper with those reached by Curtis, Fridrichsons, and Mathieson (*loc. cit.*) from *X*-ray diffraction studies on lanostenol iodoacetate. It is gratifying to find that, ***mutatis mutandis*** with regard to $C_{(15)}$ or $C_{(17)}$ for the attachment of the side chain, there is complete agreement at every relevant centre of asymmetry.

Experimental

General techniques were as in the preceding paper.

2β : 8β : 11α-*Triacetoxylanane*.—2β : 8β : 11α-Triacetoxylanan-17-one (see preceding paper) (400 mg.) was heated with hydrazine hydrate (4 ml.) and saturated ethanolic sodium ethoxide (6 ml.) at 190° for 15 hours. After working up in the usual way the product was re-acetylated and then chromatographed over alumina (Peter Spence; Grade H). Elution with 9 : 1 benzene–ether afforded 2β : 8β : 11α-*triacetoxylanane* (240 mg.), m. p. 150—151° (from methanol), $[\alpha]_D$ +18° (*c*, 1·1), $[M]_D$ +91° (Found: C, 68·85; H, 9·15. $C_{28}H_{44}O_6,CH_3{\cdot}OH$ requires C, 68·45; H, 9·5%). There was no carbonyl band in the ultra-violet spectrum.

Lanane-2 : 8 : 11-*trione*.—The foregoing triacetate (100 mg.) was hydrolysed with ethanolic potassium hydroxide, and the derived lanane-2β : 8β : 11α-triol in " AnalaR " acetic acid (10 ml.) was oxidised with chromium trioxide (100 mg.) at room temperature overnight. After working up in the usual way the product was chromatographed over alumina (Peter Spence; Grade H). Elution with 1 : 1 benzene–ether furnished the *trione* (45 mg.), m. p. 236—238° (from methanol), $[\alpha]_D$ +51° (*c*, 0·88), $[M]_D$ +175°, $\lambda_{max.}$ 285 mμ (ε, 140). It was sublimed for analysis (Found: C, 77·25; H, 9·10. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·35%).

Action of Alkali on 8 : 11-*Diketolanostanyl Acetate*.—The diketo-acetate (100 mg.), m. p. 222°, $[\alpha]_D$ +56° (*c*, 2·70), was refluxed with ethanolic potassium hydroxide (10%; 4 ml.) for 1 hour. After working up in the usual way and reacetylation with pyridine–acetic anhydride overnight at room temperature, recrystallisation from chloroform–methanol gave back starting material (65 mg.), m. p. and mixed m. p. 220—221°, $[\alpha]_D$ +56° (*c*, 2·15).

One of us (C. S. B.) is indebted to the C.S.I.R.O. (Australia) for a Research Studentship.

Birkbeck College, London, W.C.1. [*Received, October 3rd*, 1952.]

117. *A New Synthesis of Cystine and Lanthionine.*

By R. O. Atkinson, F. Poppelsdorf, and G. Williams.

The reaction of aqueous sodium sulphide and alcoholic sodium benzyl sulphide with diethyl α-acetamido-α-dimethylaminomethylmalonate methiodide yields products which on hydrolysis and decarboxylation give inactive lanthionine and inactive cystine respectively in good yield. An improved preparation of the methiodide is given, and a mechanism for the reaction is suggested.

It has been shown by Atkinson (*J.*, 1952, 3317) that diethyl α-dimethylaminomethyl-α-formamidomalonate methiodide reacts readily with hot aqueous sodium cyanide, to give diethyl α-cyanomethyl-α-formamidomalonate in good yield. Snyder and Speck (*J. Amer. Chem. Soc.*, 1939, **61**, 668, 2895) record that the following reaction takes place readily :

$$2Ph{\cdot}CH_2{\cdot}\overset{+}{N}Me_2Ph\}Cl^- + Na_2S \longrightarrow (Ph{\cdot}CH_2)_2S + 2NaCl + 2Ph{\cdot}NMe_2$$

It appeared of interest, therefore, to investigate the action of sodium sulphide on α-acetamido-α-dimethylaminomethylmalonate methiodide (I). In accordance with expectations, heating (I) with an excess of aqueous sodium sulphide yielded a product which on acid hydrolysis and decarboxylation gave inactive lanthionine in 57% yield. The reaction between (I) and excess of alcoholic potassium hydrogen sulphide, followed by hydrolysis and decarboxylation, did not, however, give cysteine, but only lanthionine. No reaction occurred when the non-quaternised base was used (cf. Snyder and Eliel, *J. Amer. Chem. Soc.*, 1948, **70**, 1703; Atkinson, *loc. cit.*).

Heating (I) with 2 mols. of sodium benzyl sulphide in ethyl alcohol for 130 hours, followed by acid hydrolysis and decarboxylation, gave *S*-benzyl-DL-cysteine in 68% yield. The latter compound was reduced with sodium in liquid ammonia and then oxidised, to give inactive cystine in 80% yield, this being a new and easy synthesis of the amino-acid. The above reactions provide a convenient method for the preparation of lanthionine and cystine having a radioactive β-carbon atom.

Since the formation of an ethylenic intermediate of (I) by elimination of amine is precluded, it is suggested that fission may occur through the agency of a proton donor by donation of an electron pair from the β-carbon atom to the nitrogen to form a highly reactive transient carbonium cation (II) (cf. Bauer, Cymerman, and Sheldon, *J.*, 1951, 3311),

(I) $(EtO_2C)_2C(NHAc){\cdot}CH_2{\cdot}NMe_3^+\}I^-$ $\qquad$ $(EtO_2C)C(NHAc){\cdot}CH_2^+$ (II)

followed by rapid addition to the sulphide or HS anion. In the latter case it appears that the desired thiol intermediate reacts more readily with the carbonium cation than does the acid sulphide, thus affording the sulphide as an end-product (cf. Snyder and Speck, *loc. cit.*).

Experimental

M. p.s are uncorrected.

Diethyl α-Acetamido-α-dimethylaminomethylmalonate Methiodide.—33% Dimethylamine solution (68 c.c.) was treated at 0° with acetic acid (75 c.c.). Diethyl acetamidomalonate (108·5 g., 0·5 mole) and 40% formaldehyde solution (41 c.c.) were added, and after 30 minutes at room temperature the mixture was cooled to −10° and made alkaline by slow addition of 20% sodium hydroxide solution. The base was extracted with ether (300 c.c.), and the extract dried (Na_2SO_4) and concentrated to 150 c.c. Methyl iodide (80 g.) was added and the mixture heated at the b. p. for 5 hours and cooled overnight. Filtration and washing with ether gave the product (144 g., 69·3%) (Found : N, 6·8; I^-, 29·9. Calc. for $C_{13}H_{25}O_5N_2I$: N, 6·75; I, 30·5%).

Inactive Lanthionine.—The methiodide (20·8 g., 0·05 mole) and sodium sulphide nonahydrate (24 g., 0·1 mole) in water (100 c.c.) were heated on a steam-bath until evolution of trimethylamine had ceased (12 hr.). The solution was concentrated to dryness *in vacuo*, and the residue was dissolved in hydrochloric acid (100 c.c.) and heated for 6 hours. Evaporation to dryness *in vacuo* and neutralisation of the aqueous solution with ammonia gave the crude amino-acid, which after dissolution in hydrochloric acid and reprecipitation with ammonia, weighed 3·0 g.

(57%) (Found: N, 13·2; S, 15·4. Calc. for $C_6H_{12}O_4N_2S$: N, 13·5; S, 15·4%). Partition chromatography on paper, with phenol as solvent, gave identical R_F values (0·19) for the material and an authentic sample of lanthionine. A solution of the material in dilute ammonia, when evaporated slowly, afforded the characteristic six-sided plates having a triangular appearance noted by Horn, Jones, and Ringel (*J. Biol. Chem.*, 1941, **138**, 141). The dibenzoyl derivative had m. p. 204—205°.

The methiodide and an excess of alcoholic potassium hydrogen sulphide (Crawhall and Elliott, *J.*, 1951, 2074) were heated on a steam-bath for 12 hours. Evaporation to dryness, followed by acid hydrolysis and decarboxylation, gave lanthionine.

S-*Benzyl*-DL-*cysteine*.—The methiodide (20·8 g., 0·05 mole) and sodium benzyl sulphide (6 g.) in ethyl alcohol (100 c.c.) were heated on a steam-bath for 130 hours. The solution was evaporated to dryness, and the residue boiled for 6 hours with concentrated hydrochloric acid (100 c.c.) Crystals of the hydrochloride separated on cooling. A solution of this in hot dilute hydrochloric acid was treated with charcoal, filtered, and neutralised with ammonia while still hot. Cooling, filtration, washing with ice-cold water, and drying, gave the product (7·3 g., 69%) m. p. 215—216° (Found: N, 6·6; S, 14·9. Calc. for $C_{10}H_{13}O_2NS$: N, 6·65; S, 15·2%). The acetyl derivative had m.p. 157—158°.

Inactive Cystine.—*S*-Benzyl-DL-cysteine (10 g.) was debenzylated with sodium in liquid ammonia and oxidised by Wood and du Vigneaud's method (*J. Biol. Chem.*, 1939, **131**, 267) to give inactive cystine (4·5 g., 80%) (Found: N, 11·5. Calc. for $C_6H_{12}O_4N_2S_2$: N, 11·65%).

We thank the Directors of the British Drug Houses Ltd. for permission to publish this work.

PRODUCTION & DEVELOPMENT DIVISION, THE BRITISH DRUG HOUSES, LTD.,
LONDON, N.1. [*Received, October 25th*, 1952].

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118. *Investigations on Natural Tannins. Part I. Acidic Condensation Reactions between Phenols and αβ-Unsaturated Carbonyl Compounds.*

By DAVID W. CLAYTON, WILLIAM E. ELSTOW, RANAJIT GHOSH, and BERTIE C. PLATT.

In the presence of acid, phenols condense with αβ-unsaturated carbonyl compounds to give six-membered heterocyclic compounds. Contrary to Adler and Tingstam (*Arkiv Kemi, Min., Geol.*, 1943, **16**, *B*, No. 18), 2 : 4-dimethylphenol and acraldehyde give 2-(2 : 4-dimethylphenoxy)-6 : 8-dimethylchroman (II). Whereas resorcinol and benzylideneacetone in methanolic hydrogen chloride at 65° yield 7-hydroxy-2-methyl-4-phenylchrom-2-en (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph), in methanolic hydrogen chloride at 40° or in ethanolic hydrogen chloride at 45° the products are 4-phenylchromans (III; R^1 = 7-OH, R^2 = Me, R^3 = OMe or OEt, R^4 = H, R^5 = Ph) (cf. G.P. 357,755). Acidic condensation of resorcinol with acraldehyde or crotonaldehyde gives chroman derivatives of type (III).

The recorded acidic condensation reactions between phenols and αβ-unsaturated carbonyl compounds are discussed with reference to two modes of interaction (A and B).

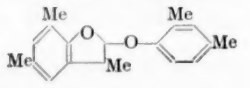
SUBSTITUTED flavans are required for an investigation of the catechin–tannin transformation. One possible synthesis appeared to be acidic condensation of phenols with αβ-unsaturated carbonyl compounds. It is generally assumed that such reactions lead to six-membered heterocyclic compounds, but Adler and Tingstam (*Arkiv Kemi, Min., Geol.*, 1943, **16**, *B*, No. 18) reported condensation of 2 : 4-dimethylphenol (2 mols.) with acraldehyde (1 mol.) in the cold under weakly acid conditions to give a five-membered ring compound, 2-(2 : 4-dimethylphenoxy)-3 : 5 : 7-trimethylcoumaran (I). The degradative evidence given in support of this structure is not flawless and the following further examination has shown that the product is 2-(2 : 4-dimethylphenoxy)-6 : 8-dimethylchroman (II).

If reaction of a dimethylphenol with acraldehyde gave a 3-methylcoumaran as

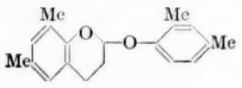
postulated by Adler and Tingstam, then that with crotonaldehyde would give a 3-ethylcoumaran; both products would possess the same terminal methyl content (Kuhn–Roth). If the products are chromans, that from acraldehyde would have no substituent at position 4, and that from crotonaldehyde a 4-methyl substituent. The terminal methyl contents of the products obtained from 2 : 4- and 3 : 4-dimethylphenol and acraldehyde under Adler and Tingstam's conditions were 14·7 and 15·3% respectively, whilst that of the product from 3 : 4-dimethylphenol and crotonaldehyde was 19·3%. This increase corresponds to one methyl group, so that the products are chromans.

Resorcinol and benzylideneacetone have been reported (Chem. Fabrik. Weiler-ter Meer, G.P. 357,755/1922) to yield 7-hydroxy-4-methyl-2-phenylchrom-3-en (VII; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph). However, we have shown that the product is a 4-phenylchroman derivative.

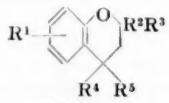
A substituted phenol and an αβ-unsaturated ketone might react according to scheme A



(I)

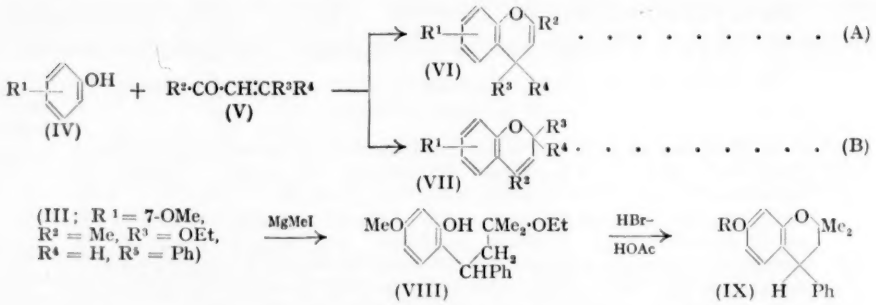


(II)



(III)

or B, of which the latter is favoured by the German workers for reaction in presence of hydrogen chloride in acetic acid. We find that resorcinol and benzylideneacetone in methanolic hydrogen chloride at 65° give a 4-phenylchrom-2-en (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph), but at 40—45° in methanolic or ethanolic hydrogen chloride give a methoxy- or ethoxy-4-phenylchroman (III; R^1 = 7-OH, R^2 = Me, R^3 = OMe or OEt, R^4 = H, R^5 = Ph), *i.e.*, in both cases according to (A). The structure of the ethoxy-



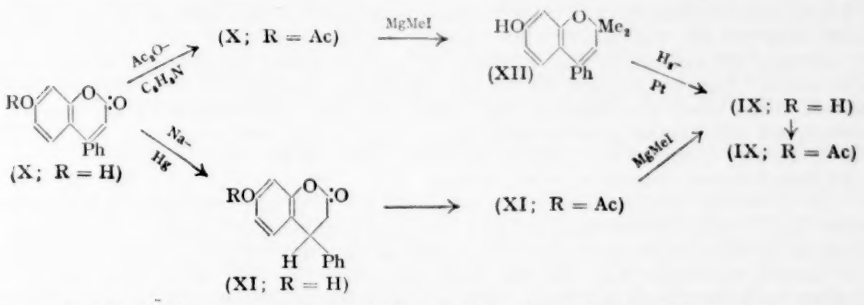
compound follows from its conversion into crystalline 7-acetoxy-2 : 2-dimethyl-4-phenylchroman (IX; R = Ac) identical (mixed m. p.) with two specimens synthesised by different, unambiguous methods. The methyl ether of the ethoxy-compound with methylmagnesium iodide gave the open-chain derivative (VIII) (formation of an acetate confirmed the opening of the pyran ring), and by demethylation and ring closure this gave (IX; R = H). Acetylation then gave the acetate (IX; R = Ac).

In our first synthesis, β-phenylumbelliferone (X; R = H) was reduced to 7-hydroxy-3 : 4-dihydro-4-phenylcoumarin (XI; R = H) (cf. Liebermann and Hartmann, *Ber.*, 1892, **25**, 2130). Acetylation and treatment with methylmagnesium iodide gave 7-hydroxy-2 : 2-dimethyl-4-phenylchroman (IX; R = H), and thence its crystalline acetate. In the second synthesis, (X; R = H) was first acetylated and then treated with methylmagnesium iodide to give 7-hydroxy-2 : 2-dimethyl-4-phenylchromen (XII), hydrogenation of which gave (IX; R = H) and thence (IX; R = Ac), m. p. 127—128°.

Resorcinol with acraldehyde or crotonaldehyde in ethanolic hydrogen chloride at 35—40° gave products which are formulated by analogy as (III; R^1 = 7-OH, R^2 = R^5 = H, R^3 = OEt, R^4 = H or Me respectively). This interpretation is supported by elementary and C-Me analyses of both the products and of a derivative.

Known acidic condensation reactions of phenols and αβ-unsaturated carbonyl compounds can be classified as occurring according to either scheme A or scheme B.

Phenol (4 or 2 mols.) and mesityl oxide (1 mol.) give 4'-hydroxy-2 : 4 : 4-trimethylflavan (III; $R^1 = H$, $R^2 = p$-HO·C_6H_4, $R^3 = R^4 = R^5 = Me$) with dry hydrogen chloride at room temperature (Dianin, *J. Russ. Phys.-chem. Soc.*, 1914, **46**, 1310; *Chem.*

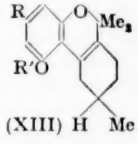


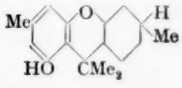
Zentr., 1915, I, 1063) or with zinc chloride under reflux (Niederl, Niederl, and Reznek, *J. Amer. Chem. Soc.*, 1936, **58**, 657); equimolecular proportions in the presence of cold concentrated sulphuric acid give 2-hydroxy-2 : 4 : 4-trimethylchroman (III; $R^1 = H$, $R^3 = R^4 = R^5 = Me$, $R^2 = OH$) which reacts further to give the dichromanyl ether (Niederl, *J. Amer. Chem. Soc.*, 1929, **51**, 2426). These reactions are based on scheme A.

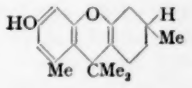
The following are examples of reactions according to scheme B. 2-(2 : 4-Dihydroxyphenyl)-4-methylpent-3-en-2-ol is reported to result from equimolecular proportions of resorcinol and mesityl oxide in the presence of hot dilute hydrochloric acid (Sen and Quadrat-i-Khuda, *J. Indian Chem. Soc.*, 1930, **7**, 167). The acid condensation of pulegone with orcinol and olivetol has been studied by Todd and his co-workers (*J.*, 1941, 137; 1942, 185) and by Adams *et al.* (*J. Amer. Chem. Soc.*, 1941, **63**, 1973). The orcinol–pulegone condensation gave a crystalline acetate, the structure of which was established as (XIII; R = Me, R' = Ac); this product was formed by scheme B. However, the possibility of reaction according to A, to give a substituted tetrahydroxanthen (XIV or XV), is not entirely precluded, since a large part of the product remained as an unidentified oil.

Whether the reaction follows route A or route B probably depends on the nature and positions of the substituents in both of the reactants. No general rule can yet be laid down, but it has been established that six-membered and not five-membered heterocyclic compounds are formed.

After these failures to synthesise flavans, phenol and resorcinol were treated with


(XIII) H Me


(XIV)


(XV)

cinnamaldehyde in methanolic hydrogen chloride, but no crystalline products were isolated.

Experimental

Microanalyses are by Drs. Weiler and Strauss, Oxford.

2-(2 : 4-*Dimethylphenoxy*)-6 : 8-*dimethylchroman* (II).—2 : 4-Dimethylphenol (10·0 g.) was treated with acraldehyde (2·7 ml.) according to Adler and Tingstam (*loc. cit.*) except that the aldehyde solution was added in one portion and the resultant mixture shaken for 2 hours before the addition of concentrated hydrochloric acid. The *chroman* (3·9 g., 34%; Adler and Tingstam give 17%) had m. p. 88° (Adler and Tingstam, 89°) (Found: C, 80·5; H, 7·8; *C*-Me, 14·7. $C_{19}H_{22}O_2$ requires C, 80·8; H, 7·8; 4*C*-Me, 21·3%).

2-(3 : 4-*Dimethylphenoxy*)-6 : 5(or 7)-*dimethylchroman*.—Acraldehyde (1 mol., 2·7 ml.) in acetic acid (3 ml.) was run into 3 : 4-dimethylphenol (2 mols., 10 g.) containing an acetic acid solution (3·2 ml.) of hydrogen chloride (0·5%), with shaking, at <5°. After 1 hour concentrated hydrochloric acid (0·3 ml.) was added and the mixture left overnight. Distillation gave a fraction, b. p. 92—120°/1 mm.; this crystallised from alcohol to give the *chroman*, m. p. 116° (Found: C, 80·5; H, 8·0; *C*-Me, 15·3%).

2-(3 : 4-*Dimethylphenoxy*)-4 : 6 : 5(or 7)-*trimethylchroman*.—Crotonaldehyde (1 mol., 3·5 ml.) in acetic acid (3·5 ml.) was caused to react with 3 : 4-dimethylphenol (2 mols., 7·1 g.) and 0·5% dry hydrogen chloride–acetic acid solution (3·5 ml.) as above (90 minutes' storage before acidification). After evaporation the residue was shaken in ether with 2N-sodium hydroxide. Removal of the ether, distillation at 154° (bath)/0·01 mm., chromatography (in benzene on alumina), and redistillation gave the *chroman*, b. p. 140° (bath)/0·003 mm., m. p. 155° (Found: C, 81·0; H, 8·3; *C*-Me, 19·3. $C_{20}H_{24}O_2$ requires C, 81·1; H, 8·1; 5*C*-Me, 25·3%).

2-*Ethoxy*-7-*hydroxy*-2-*methyl*-4-*phenylchroman* (III; R^1 = 7-OH, R^2 = Me, R^3 = OEt, R^4 = H, R^5 = Ph).—Ethanolic hydrogen chloride (3 g.; 22% w/w) was added to benzylideneacetone (4 g., 1 mol.) and resorcinol (3·2 g., 1 mol.) in dry ethyl alcohol (25 g.). After 3·5 hours' heating at 45° the solution was concentrated at 40°/20 mm. to a red syrup, which was dissolved in 2N-sodium hydroxide (150 ml.) and extracted with ether (100 ml.). This extract was extracted with 2N-sodium hydroxide (100 ml.) and the combined alkaline solutions were extracted with ether (9 × 100 ml.). The combined ethereal extracts were washed with water until neutral and dried (Na_2SO_4). After removal of the solvent, the residue (5·5 g.) was extracted with boiling light petroleum (b. p. 100—120°; 2 × 50 ml.). The colourless insoluble residue was recrystallised from aqueous alcohol, to give the *chroman*, needles, m. p. 167° (3·7 g., 45%) (Found: C, 75·8; H, 7·1. $C_{18}H_{20}O_3$ requires C, 76·0; H, 7·0%).

The *acetate*, obtained (70% yield) by use of boiling acetic anhydride (3 hours), formed needles, m. p. 101—102°, from alcohol (Found: C, 73·9; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%).

The *methyl ether*, obtained (95% yield) by means of methyl sulphate and sodium hydroxide in acetone (2 hours on the water-bath), crystallised from ether as needles, m. p. 82° (Found: C, 76·4; H, 7·4. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%).

2-*Ethoxy*-4-(2-*hydroxy*-4-*methoxyphenyl*)-2-*methyl*-4-*phenylbutane* (VIII).—A solution of 2-ethoxy-7-methoxy-2-methyl-4-phenylchroman (7·5 g., 1 mol.) in dry ether (500 ml.) was slowly added to a rapidly stirred solution of methylmagnesium iodide [4·3 mol.; from magnesium (2·4 g.) and methyl iodide (8·5 ml.)] in dry ether (300 ml.). The stirred mixture was heated under reflux for 10 hours. The ice-cooled mixture was cautiously acidified with ice-cold hydrochloric acid (400 ml. of 10%) and the ethereal layer separated. The aqueous layer was twice extracted with ether and the combined ethereal extracts were washed with 2N-sodium hydroxide (100 ml.), then with water, and dried (Na_2SO_4). Removal of the ether gave an oil (8·6 g.) which distilled at 146° (bath)/0·035 mm., to give the *phenylbutane* as a pale yellow oil (7·0 g., 88%) (Found: C, 76·6; H, 8·3. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%).

The *acetate*, obtained by means of acetic anhydride in hot pyridine (3½ hours), was a pale yellow oil, b. p. 144° (bath)/0·04 mm. (Found: C, 74·1; H, 7·7. $C_{22}H_{28}O_4$ requires C, 74·2; H, 7·9%).

7-*Acetoxy*-2 : 2-*dimethyl*-4-*phenylchroman* (IX; R = Ac).—2-Ethoxy-4-(2-hydroxy-4-methoxyphenyl)-2-methyl-4-phenylbutane (VIII) (1·1 g.) in acetic acid (15 ml.) was boiled for 1 hour with 46—48% hydrobromic acid (15 ml.). Most of the solvent was removed under reduced pressure and the residue extracted in ether with 10% sodium hydroxide solution. The alkaline solution was re-extracted once with ether and the combined ethereal extracts were washed with water until neutral and dried (Na_2SO_4). After removal of the solvent, the dark green oil (1·0 g.) was distilled. The fraction (0·35 g.) of b. p. 138—140° (bath)/0·003—0·006 mm. was treated with acetic anhydride (8 ml.) in boiling dry pyridine (8 ml.) for 3½ hours, freed from reagents by distillation under reduced pressure, dissolved in ether, and washed successively with dilute hydrochloric acid, sodium hydroxide solution (1%), and water, and dried (Na_2SO_4). Removal of the ether gave a yellow oil (0·3 g.); crystallised from alcohol this gave the *acetoxychroman* as cubes, m. p. 127—128°, alone or mixed with either of the samples synthesised as described below (Found: C, 77·2; H, 6·6. $C_{19}H_{20}O_3$ requires C, 77·0; H, 6·8%).

3 : 4-*Dihydro*-7-*hydroxy*-4-*phenylcoumarin* (XI; R = H).—7-Hydroxy-4-phenylcoumarin (X; R = H) (prepared in good yield by von Pechmann and Hanke's method, *Ber.*, 1901, **34**, 356) was reduced to the dihydrocoumarin (XI; R = H) (99%; m. p. 140°) with 2% sodium amalgam at room temperature. (Liebermann and Hartmann, *Ber.*, 1892, **25**, 2130, used a temperature of 50—60° and record m. p. 137°.)

This (1·3 g.) with acetic anhydride (5 ml.) in boiling pyridine (5 ml.) (3 hours) gave the *acetate*, rhombs, m. p. 89—91° (from methyl alcohol) (0·9 g.) (Found: C, 72·0; H, 5·0. $C_{17}H_{14}O_4$ requires C, 72·3; H, 5·0%).

7-*Hydroxy*-2 : 2-*dimethyl*-4-*phenylchroman* (IX; R = H).—The foregoing acetate (5 g., 1 mol.) in dry ether (150 ml.) was slowly added to a solution of methylmagnesium iodide [12 mols.; from magnesium (5·3 g.) and methyl iodide (13·3 ml.)] in dry ether (400 ml.). The mixture was heated under reflux for 7 hours, cooled, and cautiously acidified with 15% hydrochloric acid (500 ml.) containing ice (approx. 100 g.). The ethereal layer was separated and the aqueous layer twice extracted with ether; the combined ethereal extracts were washed with 2N-sodium hydroxide (50 ml.), then with water until neutral, and dried (Na_2SO_4). After removal of the ether the residual *chroman* (5 g.) distilled at 160° (bath)/0·03 mm. as a pale amber oil.

Its *acetate*, obtained in pyridine, crystallised from alcohol as cubes, m. p. 127—128° (Found: C, 76·8; H, 6·9%).

7-*Hydroxy*-2 : 2-*dimethyl*-4-*phenylchromen* (XII).—7-Acetoxy-4-phenylcoumarin (X; R = Ac) (5 g.; von Pechmann and Hanke, *Ber.*, 1901, **34**, 356) with excess of methylmagnesium iodide, as in the preparation of 7-hydroxy-2 : 2-dimethyl-4-phenylchroman, gave a product, b. p. 130° (bath)/0·04 mm., which, when crystallised from ether–light petroleum (b. p. 40—60°), gave the *chromen* as plates, m. p. 122·5° (2·6 g., 58%) (Found: C, 80·7; H, 6·1. $C_{17}H_{16}O_2$ requires C, 81·0; H, 6·3%). Its *acetate*, prepared in pyridine, formed plates, m. p. 91°, from alcohol (Found: C, 77·8; H, 6·1. $C_{19}H_{18}O_3$ requires C, 77·6; H, 6·1%).

7-*Hydroxy*-2 : 2-*dimethyl*-4-*phenylchroman* (IX; R = H).—The chromen (XII) (1·2 g.) in acetic acid was hydrogenated at atmospheric pressure and room temperature in the presence of Adams's platinum catalyst (0·04 g.). After 5 hours, hydrogen (absorption, 115 ml.; theor. 113 ml.) ceased to be absorbed; after filtration and evaporation under reduced pressure, the residue was shaken in ether with sodium hydrogen carbonate solution, then water, dried (Na_2SO_4), and distilled, giving a pale yellow oil, b. p. 130° (bath)/0·002 mm. (0·5 g., 41%).

Acetic anhydride in pyridine afforded the acetate as cubes, m. p. 127—128° (from methyl alcohol).

7-*Acetoxy*-2-*methoxy*-2-*methyl*-4-*phenylchroman* (III; R^1 = 7-OAc, R^2 = Me, R^3 = OMe, R^4 = H, R^5 = Ph).—Methanolic hydrogen chloride (3 g., 10% w/w) was added to a solution of resorcinol (3·9 g., 1 mol.) and benzylideneacetone (5 g., 1 mol.) in dry methyl alcohol (25 g.), and the solution kept at 40° for 4½ hours. The solvent was then removed at 40° under reduced pressure and an ethereal solution of the red residue was extracted with 2N-sodium hydroxide (8 × 50 ml.). The combined alkaline extracts were then shaken with ether (8 × 50 ml.) and the combined ethereal solutions were washed with water and dried (Na_2SO_4). Removal of the ether gave a product (1·2 g.) which distilled at 140—145° (bath)/0·09 mm. as a pale yellow oil.

Treatment with acetic anhydride in boiling pyridine (2 hours) and recrystallisation from aqueous methyl alcohol gave the *acetate* (0·6 g.), needles, m. p. 115—116° (Found: C, 73·2; H, 6·4. $C_{19}H_{20}O_4$ requires C, 73·1; H, 6·4%).

7-*Hydroxy*-2-*methyl*-4-*phenylchrom*-2-*en* (VI; R^1 = 7-OH, R^2 = Me, R^3 = H, R^4 = Ph).—The same amounts of reactants were used as in the previous experiment, but the solution was kept at 65° for 5 hours. The product, purified as described previously, gave the unsaturated *compound* as an almost colourless oil, b. p. 140—142° (bath)/0·02 mm. (Found: C, 80·5; H, 5·9. $C_{16}H_{14}O_2$ requires C, 80·7; H, 5·9%).

2-*Ethoxy*-7-*hydroxychroman* (III; R^1 = 7-OH, R^2 = R^4 = R^5 = H, R^3 = OEt).—Resorcinol (4 g., 1 mol.), acraldehyde (2 ml., 1 mol.), and ethanolic hydrogen chloride (2 ml.; 20% w/w) in dry ethyl alcohol (40 ml.) were kept at 35—40° for 4 hours. After removal of the solvent at 40° under reduced pressure, the dark oily residue was dissolved in 2N-sodium hydroxide (150 ml.) and extracted with ether (9 × 100 ml.). The combined ethereal extracts were washed with water and dried (Na_2SO_4). Removal of the solvent left an almost colourless oil (2 g.) which on distillation gave the *chroman*, b. p. 98° (bath)/0·002 mm. (Found: C, 68·0; H, 7·3; *C*-Me, 7·2. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2; 1*C*-Me, 7·7%).

The 7-*acetate*, prepared by acetic anhydride and pyridine, was an oil, b. p. 93° (bath)/0·004 mm. (Found: C, 66·2; H, 7·1; *C*-Me, 13·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8; 2*C*-Me, 12·7%).

2-Ethoxy-7-hydroxychroman (0·59 g.) with 3 : 5-dinitrobenzoyl chloride (1·17 g.) in dry pyridine (2 ml.) at 100° (½ hour) gave the 3 : 5-*dinitrobenzoate* as pale yellow needles, m. p. 113·5°, from alcohol (Found: C, 55·7; H, 4·1; N, 7·3. $C_{18}H_{16}O_8N_2$ requires C, 56·0; H, 4·2; N, 7·2%).

2-Ethoxy-7-hydroxy-4-methylchroman (III; R^1 = 7-OH, R^2 = R^5 = H, R^3 = OEt, R^4 = Me).—Ethanolic hydrogen chloride (2 ml.; 20% w/w) was added to resorcinol (4 g., 1 mol.) and crotonaldehyde (3 ml., 1 mol.) in dry ethyl alcohol (40 ml.). The solution was heated at 35—40° for 2½ hours. The *chroman*, isolated as described for 2-ethoxy-7-hydroxychroman, was an oil (2 g., 27%), b. p. 102° (bath)/0·003 mm. (Found: C, 69·5; H, 7·8; C-Me, 13·9. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7; 2*C*-Me, 14·4%).

The 3 : *5-dinitrobenzoate* crystallised as pale yellow needles, m. p. 108°, from alcohol (Found: C, 56·8; H, 4·6. $C_{19}H_{18}O_8N_2$ requires C, 56·7; H, 4·5%).

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BRITISH LEATHER MANUFACTURERS' RESEARCH ASSOCIATION,
MILTON PARK, EGHAM, SURREY. [*Received, July* 31*st*, 1952.]

119. *The Chemistry of the Triterpenes. Part XVI.* The Action of Hydrogen Chloride on Butyrospermol.*

By M. C. DAWSON, T. G. HALSALL, E. R. H. JONES, and P. A. ROBINS.

Hydrogen chloride in chloroform adds on to the *iso*propylidene group of butyrospermol and simultaneously causes the isomerisation of the unreactive double bond, probably to a position corresponding to that occupied by the double bond of *iso*lanostenyl acetate. Dehydrochlorination of the " hydrochloride " gives a butyrospermol isomer containing a vinylidene group (>C:CH$_2$).

RECENTLY the isolation of a new tetracyclic diethenoid triterpene-like alcohol, butyrospermol, was described by Heilbron, Jones, and Robins (*J.*, 1949, 444) and also by Seitz and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1626). Butyrospermol contains an *iso*propylidene grouping and an unreactive double bond, and appears to be closely related to the tetracyclic triterpenes. Basseol, a similar tetracyclic diethenoid alcohol, from shea-nut fat (Heilbron, Moffet, and Spring, *J.*, 1934, 1583), isomerises with acid to β-amyrin (Beynon, Heilbron, and Spring, *J.*, 1937, 989). The action of acidic reagents on butyrospermol was therefore of considerable interest. However, in none of our experiments has any pentacyclic compound been obtained.

When butyrospermyl acetate was treated with hydrogen chloride in chloroform an addition compound was formed (cf. Heilbron, Jones, and Robins, *loc. cit.*) and since it could not be hydrogenated it appeared probable that the *iso*propylidene double bond had reacted with the hydrogen chloride. With boiling diethylaniline there was obtained an isomer of butyrospermyl acetate, *iso*butyrospermyl acetate, from which the corresponding alcohol and hence the benzoate were prepared. Treatment of the new acetate with hydrogen chloride in chloroform regenerated the " hydrochloride."

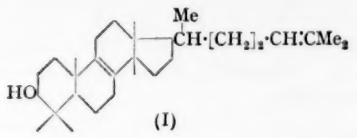
The infra-red spectrum of *iso*butyrospermyl acetate [band at 883 cm.$^{-1}$ (ms)] indicated the presence of a vinylidene group. Treatment of the acetate with osmium tetroxide yielded a complex which, after decomposition, gave a triol, and this on fission with periodic acid gave formaldehyde in good yield. Ozonolysis of *iso*butyrospermyl acetate yielded dihydroketonor*iso*butyrospermyl acetate which on hydrolysis gave the corresponding alcohol, $C_{29}H_{48}O_2$. Attempted hydrogenation of *iso*butyrospermyl acetate by using a palladium catalyst was unsuccessful, in contrast to the ready hydrogenation of butyrospermyl acetate, but with a platinum catalyst one mol. of hydrogen was taken up. The product was not dihydrobutyrospermyl acetate, but an isomer, dihydro*iso*butyrospermyl acetate.

These results clearly indicate that both double bonds are involved in the hydrogen chloride reaction. No addition occurred when dihydrobutyrospermyl acetate was treated with hydrogen chloride, but dihydro*iso*butyrospermyl acetate resulted. It was also

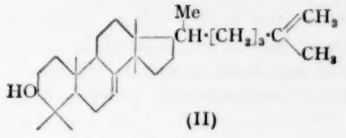
* Part XV, *J.*, 1953, 468.

obtained when the " hydrochloride " was reduced with sodium and *iso*propanol. It can thus be concluded that in the hydrogen chloride reaction, addition takes place at the *iso*propylidene group, the unreactive double bond migrates, and on dehydrochlorination hydrogen is eliminated from one of the terminal methyl groups, *i.e.*, $>C{:}CMe_2 \longrightarrow >CH{\cdot}CClMe_2 \longrightarrow >CH{\cdot}CMe{:}CH_2$.

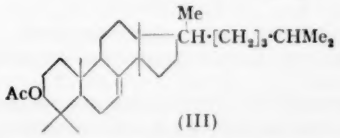
A compound analogous to the " hydrochloride " is formed under similar conditions by lanosteryl acetate, and on dehydrochlorination with alkali gives *iso*lanosterol (Dorée and Petrow, *J.*, 1936, 1562). In view of the formation of an *iso*propenyl group on dehydrochlorination of the " hydrochloride " from butyrospermyl acetate and of that from euphyl acetate (following paper), it is probable that *iso*lanosterol also contains an *iso*propenyl group and, based on the proposed structure (I) for lanosterol (Voser, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 66; Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426; Curtis, Fridricksons, and Mathieson, *Nature*, 1952, **170**, 321), is to be represented by (II). It is already known that the less reactive double bond of butyrospermol is tetrasubstituted (Seitz and Jeger, *loc. cit.*), and also that it is in a similar cyclic position to that in lanosterol (Halsall, *Chem. and Ind.*, 1951, 867). Cavalla, McGhie, and Pradhan (*J.*, 1951, 3142) and Barton, Fawcett, and Thomas (*J.*, 1951, 3147) have shown that in *iso*lanostenyl acetate (III), prepared by the action of hydrogen chloride on lanostenyl acetate, the double bond is trisubstituted and very unreactive. Hence if the carbon skeletons of butyrospermol and lanosterol are similar it is probable that the double bond in dihydro*iso*butyrospermol is trisubstituted as in *iso*lanostenol.



(I)



(II)



(III)

Perbenzoic acid titration of some of the above compounds under identical conditions revealed that with those subjected to hydrogen chloride treatment, the rate of absorption of oxygen by the less reactive ethylenic linkage was extremely slow and far from complete (Table 1).

TABLE 1.

Atoms oxygen absorbed after :	1	3	9	23 days
Butyrospermyl acetate	1·15	1·9	1·9	—
Dihydro*iso*butyrospermyl acetate	0·05	0·1	0·15	0·15
Dihydrobutyrospermyl acetate	0·95	1·0	1·05	—
Butyrospermyl acetate " hydrochloride "	0	0	0·05	0·2
*iso*Butyrospermyl acetate	0·95	1·05	1·10	1·05

The ultra-violet absorption of compounds of the dihydro*iso*-series has been determined in the 2000—2250 Å region (Table 2) and is consistent with the presence of a trisubstituted double bond (cf. Bladon, Henbest, and Woods, *J.*, 1952, 2737; Halsall, *loc. cit.*).

TABLE 2.

$\varepsilon_{obs.}$ in alcohol at :	2100 Å	2150 Å	2200 Å	2230 Å
Dihydrobutyrospermol	4200	3200	1900	1000
Dihydrobutyrospermyl acetate	4100	3100	1800	800
Dihydro*iso*butyrospermol	5100	3100	1550	—
Dihydro*iso*butyrospermyl acetate	4300	2700	1400	700

In view of both the extreme unreactivity of the double bond in dihydro*iso*butyrospermol towards per-acid, especially when compared with that of *iso*euphenyl acetate (cf. following

paper), and the ultra-violet absorption data, it is reasonable to conclude that the new double bond corresponds in environment to that in *iso*lanostenyl acetate.

When preparing butyrospermyl acetate from shea-nut fat great difficulty was experienced in eliminating β-amyrin acetate, and it was possible to obtain samples of seemingly nearly pure butyrospermyl acetate, m. p.s *ca.* 140—143° (*i.e.*, 3—4° low) [$(\alpha)_D$ *ca.* +20°], still containing 15—20% of β-amyrin acetate. We have failed repeatedly in attempts to obtain further samples of basseol, and recently Dr. G. D. Meakins has examined samples of fat from many different varieties of shea-nuts but in no case has any evidence of the presence of basseol been obtained. It must be considered whether the original basseol acetate was not in fact butyrospermyl acetate contaminated with β-amyrin acetate. The constants reported for basseol acetate (m. p. 141°; $[\alpha]_D$ +22·4°) agree well with those of our contaminated butyrospermyl acetate fractions, *i.e.*, a β-amyrin acetate content of *ca.* 16%. The presence of the β-amyrin acetate could explain the isolation of some of this compound in the isomerisation reactions, but the yields would be well below some of those described by the previous workers. Another possibility which needs further consideration is that the original fat emanated from a source other than shea-nuts.

A major difficulty in working with butyrospermol is the tedious isolation procedure. It forms only a few % of the non-saponifiable matter of shea-nut fat, and this in turn constitutes only 5—7% of the whole fat. It has now been found that, by allowing the fat to crystallise from an acetone solution at −80°, the non-saponifiable content remaining in solution is raised to about 60% (cf. Hilditch and Ichaporia, *J. Soc. Chem. Ind.*, 1938, **57**, 44).

Bauer and Moll (*Fette u. Seifen*, 1939, **46**, 530) reported the isolation of a new alcohol (parkeol), m. p. 164°, from shea-nut fat. In the present work an alcohol which is probably parkeol has been isolated. It has a similar m. p. (162—165°) and that of its acetate (154—157°) agrees with the m. p. of parkeyl acetate (154°).

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. The alumina used for chromatography had an activity of I—II unless otherwise stated.

Preparation of the "Hydrochloride" from Butyrospermyl Acetate.—A solution of butyrospermyl acetate (500 mg.) in chloroform (15 c.c.) was cooled to 0° and a slow stream of dry hydrogen chloride was passed in for 2 hours. Evaporation under reduced pressure yielded a residue which was crystallised from ethanol to give the "*hydrochloride*" as needles, m. p. 139—141°, $[\alpha]_D^{19}$ +34° (*c*, 1·5) (Found : C, 76·0; H, 10·45. $C_{32}H_{53}O_2Cl$ requires C, 76·05; H, 10·55%). It gave a pale yellow colour with tetranitromethane.

iso*Butyrospermyl Acetate.*—The crude "hydrochloride" [obtained from butyrospermyl acetate (1 g.)] in diethylaniline (15 c.c.) was heated under reflux for 1 hour. The product was isolated with light petroleum (b. p. 40—60°) and yielded iso*butyrospermyl acetate* as needles (450 mg.) (from ethanol), m. p. 106—107·5°, $[\alpha]_D^{23}$ +34° (*c*, 1·6) (Found : C, 82·3; H, 11·15. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%). After 48 hours at 20° in sufficient ethanolic potassium hydroxide (10%) to effect solution, the acetate yielded iso*butyrospermol*, as fine needles [from light petroleum (b. p. 40—60°)], m. p. 60—67°, $[\alpha]_D^{16}$ +29° (*c*, 0·9) (Found : C, 83·9; H, 11·8. $C_{30}H_{50}O$ requires C, 84·45; H, 11·8%). The *benzoate*, prepared by benzoylation in pyridine, formed leaflets (from ethanol), m. p. 149—152°, $[\alpha]_D^{16}$ +60° (*c*, 0·8) (Found : C, 83·5; H, 10·25. $C_{37}H_{54}O_2$ requires C, 83·75; H, 10·25%).

Dihydroisobutyrospermyl Acetate.—(*a*) *iso*Butyrospermyl acetate (200 mg.) in methyl acetate (25 c.c.) was shaken with pre-reduced Adams's catalyst (20 mg.) and hydrogen at 20° until absorption of hydrogen ceased. After filtration and evaporation, elution of the residue with benzene–light petroleum (b. p. 60—80°) (1 : 19) from alumina (30 g.) yielded a fraction which was crystallised from ethanol, giving *dihydroisobutyrospermyl acetate* in good yield as needles, m. p. 125·5—127°, $[\alpha]_D^{18}$ +33° (*c*, 1·5) (Found : C, 82·0; H, 11·6. $C_{32}H_{54}O_2$ requires C, 81·65; H, 11·55%).

(*b*) Dihydrobutyrospermyl acetate (200 mg.) in chloroform (10 c.c.) was treated with hydrogen chloride as above. The product on crystallisation from aqueous ethanol gave dihydro-*iso*butyrospermyl acetate as needles (150 mg.), m. p. 124—127°, $[\alpha]_D^{18}$ +33°, identical with the product obtained by method (*a*).

(*c*) Butyrospermyl acetate " hydrochloride " (100 mg.) in *iso*propanol (25 c.c.) was treated with sodium (1·8 g.), and the mixture then heated at 100° for 1·5 hours. After the addition of ethanol (10 c.c.) the mixture was poured into excess of dilute acetic acid, and the product, isolated with ether, was acetylated at 20° in pyridine. Evaporation of the pyridine under reduced pressure and crystallisation of the residue from ethanol gave dihydro*iso*butyrospermyl acetate as needles (80 mg.), m. p. 124—127° undepressed on admixture with a sample obtained by method (*a*).

Action of Osmium Tetroxide on iso*Butyrospermyl Acetate.*—The acetate (1·0 g.) in dry ether (50 c.c.) was treated with osmic acid (550 mg.), and the solution kept at 20° for 7 days. The solution was evaporated to dryness under reduced pressure, and the residue refluxed for 4 hours with mannitol (3·2 g.) in ethanol (40 c.c.), benzene (40 c.c.), and potassium hydroxide (2 g.) dissolved in a little water. Dilution with dilute acetic acid and isolation with ether yielded a solid which was fractionated on deactivated alumina (activity III—IV; 25 g.). The fraction eluted with benzene–ether (4 : 1 and 1 : 1) gave the *triol*, crystallising from nitromethane as fine needles (250 mg.), m. p. 182—184°, $[\alpha]_D^{20}$ +19° (*c*, 1·3) (Found : C, 78·3; H, 11·3. $C_{30}H_{52}O_3$ requires C, 78·2; H, 11·4%).

Periodic Acid Fission of the Triol.—The triol (85 mg.) in methanol (6 c.c.) was treated with periodic acid (175 mg.) in water (3 c.c.), and set aside overnight at 20°. Water (10 c.c.) was then added and the whole distilled until 7·5 c.c. of distillate had been collected. Water (10 c.c.) was again added and a further 7·5 c.c. of distillate was collected. To each distillate was added a solution of 2 : 4-dinitrophenylhydrazine (1 g.) in sulphuric acid (4N; 45 c.c.). After an hour the distillates were extracted with benzene, and the extracts washed and dried. Chromatography of the extract of the first distillate gave no characterisable product. Chromatography of the extract of the second distillate gave formaldehyde 2 : 4-dinitrophenylhydrazone (35 mg.), m. p. 162—165° undepressed on admixture with an authentic specimen.

Ozonolysis of iso*Butyrospermyl Acetate.*—A solution of *iso*butyrospermyl acetate (1·2 g.) in ethyl acetate (50 c.c.) was cooled to −78°, and to it was added a saturated solution of ozone in ethyl acetate at −78° (35 c.c.) until a faint blue colour remained. The mixture was allowed to warm to 20° and the ethyl acetate was then evaporated under reduced pressure. The residue was taken up in benzene–light petroleum (1 : 9) and adsorbed on alumina (1200 g.). Elution with benzene gave a solid, crystallisation of which from ethyl acetate–methanol yielded *dihydroketonor*iso*butyrospermyl acetate* as needles (0·3 g.), m. p. 128—131°, $[\alpha]_D^{20}$ +31° (Found : C, 79·2; H, 10·7. $C_{31}H_{50}O_3$ requires C, 79·1; H, 10·7%). Hydrolysis of the acetoxy-norketone (54 mg.) in 1% methanolic potassium hydroxide (2 c.c.) for 96 hours at 20° gave *dihydroketonor*iso*butyrospermol* in good yield as needles from aqueous methanol, m. p. 169·5—173°, $[\alpha]_D^{20}$ +17° (Found : C, 81·1; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·25; H, 11·3%).

Isolation of Parkeol.—The non-saponifiable fraction (223 g.) of shea-nut fat was heated under reflux for 1½ hours with acetic anhydride. The mixture was kept at 20° for 18 hours, and the large mass of sticky solid which had formed was then filtered off. During the filtration more crystals (20 g.) separated from the filtrate. These were isolated and adsorbed from light petroleum (b. p. 60—80°) on alumina(1300 g.). After elution with light petroleum (b. p. 60—80°)–benzene (1 : 1), to remove butyrospermyl and β-amyrenyl acetates, elution with benzene gave a fraction (2·6 g.) which was crystallised several times from ethyl acetate–ethanol giving parkeyl acetate as needles, m. p. 154—157°, $[\alpha]_D^{20}$ +95° (Found : C, 82·05; H, 11·3. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Hydrolysis of the acetate with 12% methanolic potassium hydroxide gave parkeol, needles (from alcohol), m. p. 162—165°, $[\alpha]_D^{20}$ +65°.

Thanks are proffered to Mr. E. S. Morton and Mr. H. Swift for the majority of the microanalyses. The other analyses were carried out by Messrs. Weiler and Strauss. The authors are indebted to Dr. G. D. Meakins for his assistance with the infra-red spectra determinations, and also for permission to mention the results of his studies on samples of shea-nut fat. Two of the authors (P. A. R. and M. C. D.) thank the Department of Scientific and Industrial Research for a Senior Research Award and a maintenance grant, respectively.

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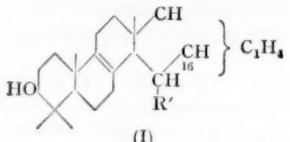
120. *The Chemistry of the Triterpenes. Part XVII.* Some Aspects of the Chemistry of Tetracyclic Triterpenes.*

By M. C. Dawson, T. G. Halsall, and R. E. H. Swayne.

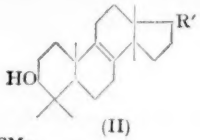
The action of chloroformic hydrogen chloride on euphenyl and euphadienyl acetates is described and the chemistry of the resulting isomerisation products is discussed.

The tetracyclic triterpenes are classified into two groups on the basis of both rotation and ultra-violet absorption data.

To determine whether the effect of chloroformic hydrogen chloride on butyrospermyl acetate (Dawson, Halsall, Jones, and Robins, preceding paper) and lanosteryl acetate (Dorée and Petrow, *J.*, 1936, 1562) was of a general nature, its action on euphyl (euphadienyl) acetate has been investigated. A chlorine-containing product was obtained which on dehydrochlorination gave *iso*euphadienyl acetate. The infra-red spectrum [band at 886 cm.$^{-1}$ (ms)] showed that a vinylidene group was present and this was confirmed by ozonolysis. Hydrogenation gave *iso*euphenyl acetate, identical with that obtained by Vilkas, Dupont, and Dulou (*Bull. Soc. chim.*, 1949, 813) by the action of hydrochloric acid in acetic acid on dihydroeuphyl acetate (euphenyl acetate). Hydrolysis of *iso*euphenyl acetate in the cold gave *iso*euphenol, isolated as a crystalline solid. Oxidation gave *iso*euphenone, characterised as its oxime. *iso*Euphenyl acetate was also obtained by the

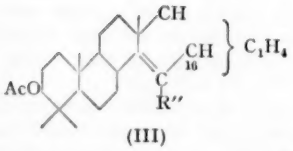


(I)

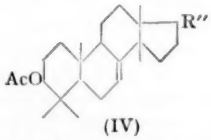


(II)

R′ = ·CHMe·[CH$_2$]$_2$·CH:CMe$_2$



(III)



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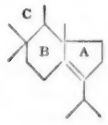


(V)

R″ = ·CHMe·[CH$_2$]$_3$·CHMe$_2$

action of chloroformic hydrogen chloride on dihydroeuphyl acetate. Hence the behaviour of euphyl acetate is similar to that of butyrospermyl and lanosteryl acetates, *i.e.*, isomerisation of the less reactive double bond, and addition of hydrogen chloride to the *iso*propylidene group. Further, as proved in the case of butyrospermol and suspected for lanosterol, dehydrochlorination yields an *iso*propenyl, rather than an *iso*propylidene group.

Since the above work was carried out, Christen, Dunnenberger, Roth, Heusser, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 1756) have proposed structure (I) for euphol in which the double bond is situated in a somewhat different environment from that in lanosterol (II) (Curtis, Fridricksons, and Mathieson, *Nature*, 1952, **170**, 1321; Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426), and (III) for *iso*euphenyl acetate. The work of Vilkas (*Bull. Soc. chim.*, 1950, 582) on *iso*euphenyl acetate indicated that its double bond was differently situated from that in *iso*lanostenyl acetate (IV) (Barton, Fawcett, and Thomas, *J.*, 1951, 3147; Cavalla, McGhie, and Pradhan, *J.*, 1951, 3142); and this has been confirmed by an examination of the low wave-length ultra-violet absorption of *iso*euphenyl acetate (Table 1) (cf. Bladon, Henbest, and Wood, *J.*, 1952, 2737; Halsall, *Chem. and Ind.*, 1951, 867). Whilst the intensity values for dihydro*iso*butyrospermol and its acetate are a little lower than those of dihydrobutyrospermol and its acetate (preceding

* Part XVI, preceding paper.

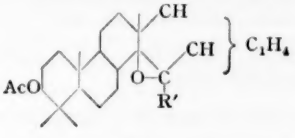
paper), those for *iso*euphenyl acetate are considerably higher than the corresponding values for euphenyl acetate. They definitely indicate that the double bond in *iso*euphenyl acetate is tetrasubstituted and, further, they strongly suggest that it is exocyclic to one ring, but not to two as with the double bond of δ-amyrenyl acetate. The correlation with the intensity values for the isomer (partial formula V) obtained from γ-lupene by Nowak, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1949, **32**, 323) is very striking. This isomer is an exact model for comparison purposes, the double bond being in a position corresponding

TABLE 1.

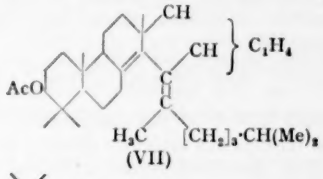
$\varepsilon_{obs.}$ in alcohol at :	2100 Å	2150 Å	2200 Å	2230 Å
Euphenyl acetate	5000	2700	1000	400
*iso*Euphenyl acetate	7200	4400	2000	900
Isomer from γ-lupene	6600	4500	2500	1300
δ-Amyrenyl acetate	7700	5300	4200	—

to that in structure (III) for *iso*euphenyl acetate. An interesting comparison may be drawn between the acidic isomerisation of euphenyl acetate and that of $\Delta^{8(9)}$-cholestenol to $\Delta^{14(15)}$-cholestenol (Wieland and Görnhardt, *Annalen*, 1947, **557**, 248).

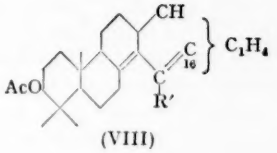
Oxidation of *iso*euphenyl acetate with chromic acid under mild conditions gave a compound, $C_{32}H_{54}O_3$, which showed no light absorption of appreciable intensity above 2100 Å, and is identical with the epoxide (VI) described by Vilkas and the Swiss workers. Treatment with ethanolic hydrogen chloride yielded the diene previously obtained from *iso*euphenyl acetate oxide by Christen *et al.* (*loc. cit.*), with maximal absorption at 2470, 2555, and 2650 Å (ε = 18,200, 21,400, and 13,200, respectively). The Swiss workers put forward two structures (VII) and (VIII) for their diene. The chromophores present in



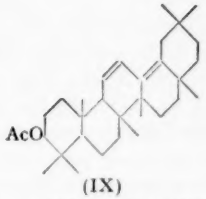
(VI)



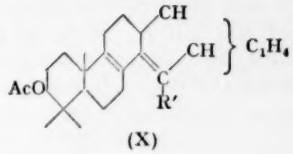
(VII)



(VIII)



(IX)



(X)

R′ = ·CH(Me)·[CH$_2$]$_3$·CH(Me)$_2$

these two formulations would be expected to have different, but characteristic ultra-violet absorption properties. The *cisoid* chromophore of (VII) should give rise to a relatively low maximum intensity of absorption corresponding to ε = *ca.* 10,000 at 2600—2650 Å, whilst for (VIII) with a *transoid* chromophore the corresponding value of ε would be *ca.* 25,000 at 2500—2550 Å (cf. the discussion of the absorption spectra of dehydro- and *iso*dehydro-oleanolic acids by Barton and Brooks, *J.*, 1951, 261). Inspection of the spectrum of the diene from *iso*euphenyl acetate epoxide, with its high ε of 22,000, shows that (VII) may be discounted. The chromophore of (VIII) is very similar to that of β-amyradienyl-II acetate (olea-11 : 13-dien-2″β″-yl acetate) (IX) [$\lambda_{max.}$ 2430, 2510 (ε = 31,000), 2600 Å; Green, Mower, Picard, and Spring, *J.*, 1944, 527], the only difference being the further substitution of the diene system of (VIII) by at least one more carbon substituent. The positions of the maxima in the spectrum of (VIII), assuming only one further substituent on the diene system than in (IX) and hence that a hydrogen atom is attached to $C_{(16)}$, should be 40—50 Å nearer to the visible than those of (IX). The spectrum of the diene from *iso*euphenyl acetate oxide does in fact show this shift. This confirms that (VIII) rather than (VII) is the probable structure of the diene, and indicates that one

hydrogen atom is attached to $C_{(16)}$ of the diene and that two are attached to $C_{(16)}$ of euphol. The ultra-violet data would be equally consistent with (X), but this structure provides a far less satisfactory basis for explaining the course of the hydrogenation of the diene (cf. Christen *et al.*, *loc. cit.*).

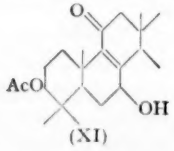
TABLE 2. *Tetracyclic triterpenes.*

	A	B	C	D		
				Main max., Å		
Euphenol	+116° [1]	−479° [2]	−595°	2325	2400	— [2]
Euphenyl acetate	+165 [1]	−429 [2] *	−594	2330	2400	2475 [2]
Euphorbenol	− 9 [3]	−579 [2]	−570	2320	2390	— [2]
Euphorbenyl acetate	± 0 [3]	−650 [2]	−650	2320	2390	— [2]
Tirucallenol	+ 13 [4]	−697 [2]	−710	2325	2400	— [2]
Tirucallenyl acetate	− 54 [4]	−634 [2]	−580	2325	2375	— [2]
Methyl acetyldihydro-α-elemolate	−169 [5]	−590 [6]	−421	2320	2390	2470 [6]
Lanosterol	+258 [9]	+326 [7]	+ 68	—	—	—
Lanosteryl acetate	+306 [9]	+410 [7]	+104	—	—	—
Dihydrolanosterol	+260 [9]	+286 [10]	+ 26	—	—	—
Dihydrolanosteryl acetate	+275 [9]	+411 [10]	+136	2360 2380	2430 2450	2510 2500 } [8]
Methyl acetyldihydroeburicoate	+288 [11]	+302 [11]	+ 14	—	2430	2510 [11]

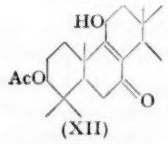
Column headings: A, $[M]_D$ of the triterpene; B, $[M]_D$ of the corresponding dehydro-derivative; C, $\Delta[M]_D$ for the conversion of the triterpene into its dehydro-derivative; D, $\lambda_{max.}$ of the corresponding dehydro-derivative. [1] Jeger and Krüsi, *Helv. Chim. Acta*, 1947, **30**, 2047. [2] Barbour, Bennett, and Warren, *J.*, 1951, 2540. [3] Vogel, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 510. [4] Haines and Warren, *J.*, 1949, 2554. [5] Ruzicka, Rey, and Spillman, *Helv. Chim. Acta*, 1942, **1375**. [6] Halsall, Jones, and Swayne (unpublished results). [7] Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. [8] Dorée, McGhie, and Kurzer, *J.*, 1949, 570. [9] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1945, **28**, 759. [10] Ruzicka, Denss, and Jeger, *Helv. Chim. Acta*, 1946, **29**, 204. [11] Lahey and Strasser, *J.*, 1951, 873.

* Barbour, Bennett, and Warren (*loc. cit.*) quote a rotation $[\alpha]_D$ −9·16°. This is almost certainly a misprint for −91·6°; our calculations are based on this latter figure.

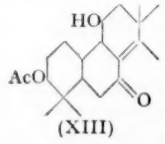
For some time evidence has been accumulating which permits a classification of the tetracyclic triterpenes into two groups, one typified by lanosterol and the other by euphol. With the first, dehydrogenation at two of the carbon atoms at positions α to the unreactive double bond and the formation of a diene results in a positive change of rotation, whilst the main absorption maximum of the diene is at 2430—2450 Å, with subsidiary maxima at 2380 and 2510 Å. With the second group a very large negative change of rotation occurs whilst the main maximum is found at *ca.* 2390 and the subsidiary maxima at 2320 and *ca.* 2470 Å (Table 2). Into the first group fall lanosterol, eburicoic acid, and (from data which



(XI)



(XII)



(XIII)

are not yet complete) possibly polyporenic acids A and C. Into the second fall euphol, euphorbol, tirucallol, and α-elemolic acid.

In connection with this classification it is of interest that the catalytic reduction of diketoeuphenyl acetate, diketoeuphorbenyl acetate (Barbour and Warren, *Chem. and Ind.*, 1952, 295), and methyl acetyl*iso*elemenadionolate (Ruzicka, Rey, Spillman, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1659) leads in each case to the formation of an αβ-unsaturated ketone with maximal absorption of only moderate intensity (ε <10,000) at about 2580—2600 Å. The chromophoric systems are probably identical in each case, but the structures of these unsaturated ketones are not clear. In the case of euphol the two partial structures (XI) and (XII) are the most obvious, but these should give rise to a maximum at about 2500 Å (*cf.* 7-ketoergost-8-en-3-yl acetate with $\lambda_{max.}$ 2520 Å, ε 10,000). A more likely alternative structure is (XIII) for which the calculated maximum would be 2590 Å [*cf.* also 3 : 7-diketoergost-8(14)-en-5-ol, $\lambda_{max.}$ 2540 Å (in ether) corresponding to

$\lambda_{max.}$ 2610 Å (in alcohol), log ε 4·0, and 15-ketoergost-8(14)-en-3-yl acetate, $\lambda_{max.}$ 2590 Å, log ε 4·1] which agrees much better with the observed value of 2580—2600 Å. Further the low intensity values would be compatible with the *cisoid* chromophore of (XIII). Its formation during the hydrogenation process would involve a migration of the double bond, but this is analogous to the behaviour of the 8 : 9-double bond in zymosterol on hydrogenation with platinum–acetic acid, resulting in the formation of $\Delta^{8(14)}$-cholestenol (cf. Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., pp. 289, 290). If (XIII) is the correct structure for these hydroxy-ketones then a reversed double bond shift occurs on chromic oxidation in the euphol series, for diketoeuphenyl acetate is produced.

Experimental

M.p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. The alumina used for chromatography had an activity of I—II.

iso*Euphadienyl Acetate*.—Euphadienyl acetate (400 mg.) was dissolved in chloroform (40 c.c.), and a slow stream of dry hydrogen chloride was passed through for 5 days at 20°, the reaction being followed by measurement of the optical activity of the solution. Evaporation under reduced pressure then yielded a viscous oil which gave a positive test for halogen. Diethylaniline (6 c.c.) was added and the mixture heated under reflux for 1½ hours. The product was isolated with light petroleum (b. p. 60—80°) and the solution, after it had been washed and dried, was adsorbed on a column of alumina (35 g.). Elution with benzene–light petroleum (b. p. 60—80°) (1 : 9) gave a fraction which yielded iso*euphadienyl acetate* as platelets (from methanol) (275 mg.), m. p. 96—98°, $[\alpha]_D^{20}$ −10° (*c*, 1·3) (Found: C, 81·75; H, 11·3. $C_{32}H_{52}O_2$ requires C, 82·0; H, 11·2%).

iso*Euphenyl Acetate*.—(*a*) Euphenyl acetate (310 mg.) was dissolved in chloroform (35 c.c.) and a slow stream of dry hydrogen chloride was passed through for 4 days, the reaction being followed by the change in the optical activity of the solution. The chloroform was then evaporated under reduced pressure and the residue was crystallised from methanol–ethyl acetate to give *iso*euphenyl acetate, m. p. 112—113°, $[\alpha]_D^{20}$ −9° (*c*, 1·4). Christen *et al.* (*loc. cit.*) give m. p. 113°, $[\alpha]_D$ −10°.

(*b*) *iso*Euphadienyl acetate (380 mg.) in acetic acid (60 c.c.) was shaken with hydrogen at 20° in the presence of Adams's catalyst (30 mg.) until absorption was complete. After filtration and evaporation of the filtrate under reduced pressure, the residue was crystallised from methanol to give *iso*euphenyl acetate, m. p. 113—114°, $[\alpha]_D^{20}$ −7° (*c*, 1·0), identical with that prepared by method (*a*). Hydrolysis of the acetate (260 mg.) with methanolic potassium hydroxide (1%; 50 c.c.) at 20° for 100 hours gave *iso*euphenol which crystallised with difficulty from nitromethane; it had m. p. 98—101°, $[\alpha]_D^{20}$ −20° (*c*, 1·15) (Found: C, 83·5; H, 12·05. Calc. for $C_{30}H_{52}O$: C, 84·05; H, 12·2%. Chromic acid in acetone (8N) was added to *iso*euphenol (≡ 380 mg. of *iso*euphenyl acetate) until a faint brown colour remained. The product, isolated with ether, was a gum, $[\alpha]_D^{20}$ +24° (*c*, 1·5). Oximation of the gum gave iso*euphenone oxime* as needles (ethanol–water), m. p. 142—143° (Found: N, 3·0, 3·3. $C_{30}H_{51}ON$ requires N, 3·15%).

Ozonolysis of iso*Euphadienyl Acetate*.—A solution of *iso*euphadienyl acetate (650 mg.) in ethyl acetate (20 c.c.) was cooled to −78° and to it was added a saturated solution of ozone in ethyl acetate at −78° until a faint blue coloration remained. The mixture was allowed to warm to 20° and was then refluxed for 2 hours with Raney nickel, nitrogen being passed through the solution. The issuing gases were passed through an aqueous solution of dimedone which was kept for 16 hours at 0°. The dimedone derivative was collected, dried (75 mg.), and crystallised from aqueous ethanol. The m. p., 188°, was undepressed on admixture of the sample with an authentic specimen of formaldehyde dimedone.

Oxidation of Hydroxyketoeuphenyl Acetate.—To a solution of hydroxyketoeuphenyl acetate (140 mg.) (m. p. 184—189°) in acetone (12 c.c.) a solution of chromic acid in acetone (0·8N) was added dropwise until a faint brown coloration remained. After 2 minutes, dilution with water and extraction with ether yielded a product (130 mg.), crystallisation of which from methanol gave diketoeuphenyl acetate as needles, m. p. 109—113° undepressed on admixture with an authentic specimen of m. p. 111—114°. $\lambda_{max.}$ 2735 Å; ε = 8,500.

iso*Euphenyl Acetate Epoxide*.—To a solution of *iso*euphenyl acetate (1·5 g.) in acetic acid (90 c.c.) at 20°, a solution of chromic acid (2·7 g.) in acetic acid (90%; 30 c.c.) was added. After 10 minutes, dilution with water and extraction with ether yielded a product (1·5 g.)

which was adsorbed from light petroleum (b. p. 60—80°)–benzene (1 : 1) on alumina (150 g.). Elution with benzene gave *iso*euphenyl acetate epoxide (740 mg.) which crystallised from methanol as plates, m. p. 119·5—121°, $[\alpha]_D^{21}$ +7° (*c*, 1·2) (Found: C, 78·75; H, 11·5. Calc. for $C_{32}H_{54}O_3$: C, 79·0; H, 11·2%). A further preparation gave *iso*euphenyl acetate epoxide as plates, which melted at 109—111°, followed by crystallisation of the melt and remelting at 137—139°. The melting point (138—140°) of an authentic specimen of *iso*euphenyl acetate epoxide prepared by the action of perbenzoic acid on *iso*euphenyl acetate was not depressed on admixture of the authentic specimen with either of the samples prepared by chromic acid oxidation. Christen *et al.* (*loc. cit.*) give m. p. 134°, $[\alpha]_D$ +6°.

Action of Ethanolic Hydrogen Chloride on iso*Euphenyl Acetate Epoxide.*—A solution of the epoxide (145 mg.) in ethanol (12 c.c.) and concentrated hydrochloric acid (1 c.c.) was heated under reflux for 2 hours. Dilution with water and extraction with ether yielded a gummy residue which was acetylated at 20° for 16 hours with pyridine (2 c.c.) and acetic anhydride (2 c.c.). The acetylated product was dissolved in benzene and adsorbed on alumina (20 g.). Elution with benzene gave the diene (110 mg.), plates (from methanol), m. p. 91—93°, $[\alpha]_D^{19}$ +18° (*c*, 0·25), $\lambda_{max.}$ 2470, 2555, and 2650 Å; ε 18,300, 21,500, and 13,000, respectively. Christen *et al.* (*loc. cit.*) give m. p. 91—92°, $[\alpha]_D$ +17°.

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THE UNIVERSITY, MANCHESTER, 13. [*Received, October* 13*th*, 1952.]

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121. *The Action of Acyl Cyanides on* 2- *and* 1 : 2-*Substituted Indoles. Part I.*

By A. K. KIANG and FREDERICK G. MANN.

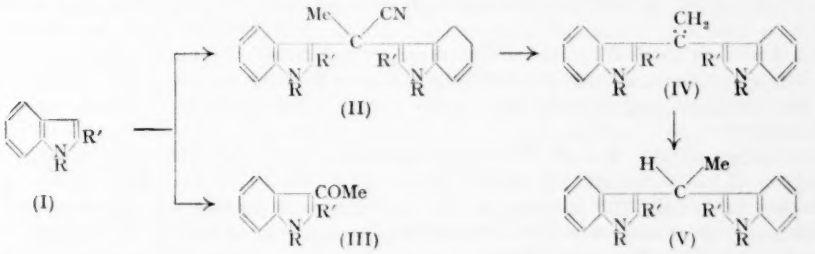
Acetyl and benzoyl cyanides react with the above indoles in the presence of hydrogen chloride usually to give bis-3-indolyl derivatives of type (II) and (IX), whereas in the presence of pyridine the 3-acylindole is formed. No indication that these acyl cyanides undergo a Hoesch-type reaction with the above indoles could be obtained. Acetyl cyanide, however, reacts apparently abnormally with 2-phenylindole to give α-(2-phenyl-3-indolyl)acrylonitrile.

The products obtained by heating the bis-3-indolyl derivatives with soda-lime and with ethanolic potassium hydroxide have been investigated in some detail, particularly with regard to their structure and their behaviour towards acids and alkalis.

IN an investigation, to be described in a later paper, on the action of acyl cyanides on substituted indoles which possessed several potential points of reaction, some apparently anomalous results were obtained. It became clear that, before these results could be satisfactorily interpreted, the action of acyl cyanides on simpler indoles containing non-reactive substituents in the 2- and 1 : 2-positions must be studied. The results of this preliminary investigation are recorded in the present paper. The action of acetyl cyanide on certain alkyl- and aryl-indoles is described first, followed by that of benzoyl cyanide.

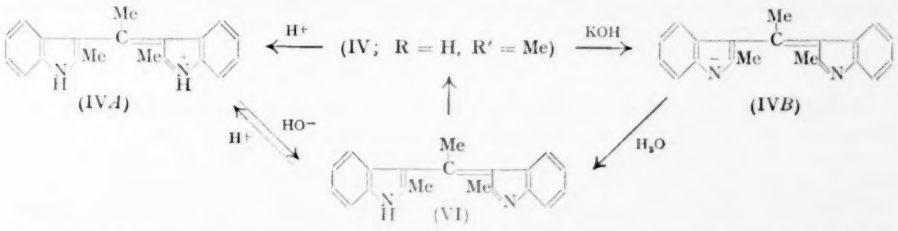
When 2-methylindole (I; R = H, R′ = Me) was treated with an equimolecular quantity of acetyl cyanide in pure chloroform at room temperature for 24 hours or for 40 minutes under reflux, the main product was the colourless crystalline 1-cyano-1 : 1-di-(2-methyl-3-indolyl)ethane (II; R = H, R′ = Me), a smaller quantity of 3-acetyl-2-methylindole (III; R = H, R′ = Me) being also formed. However, in the presence of a small proportion of hydrogen chloride, at room temperature or under reflux, the ethane (II; R = H, R′ = Me) was formed to the apparently complete exclusion of the acetylindole. (When the chloroform solution of the indole and the cyanide was saturated with hydrogen chloride, a heavy tar was deposited, from which no crystalline material could be isolated.)

Conversely, when the original solution in pure chloroform was diluted with a trace of pyridine and then boiled, the acetylindole (III; R = H, R′ = Me) was formed to the exclusion of the ethane. These results clearly indicate the effects of acid and alkali.



The structure of the ethane (II; R = H, R′ = Me) is confirmed by its infra-red spectrum, which shows the characteristic –NH– and –CN absorption bands at 2·9 and 4·53 μ respectively. The compound is unaffected by cold hydrochloric acid: when, however, it is heated in a vacuum (alone or mixed with soda-lime) or boiled with aqueous-ethanolic potassium hydroxide, hydrogen cyanide is lost with the formation of 1 : 1-di-(2-methyl-3-indolyl)ethylene (IV; R = H, R′ = Me), apparently identical with the compound prepared from 2-methylindole by Angeli and Marchetti (*Atti R. Accad. Lincei*, 1907, **16**, ii, 790) by the action of ethyl acetate and sodium ethoxide and by Borsche and Groth (*Annalen*, 1941, **549**, 244) by the action of boiling acetyl chloride, and which has hitherto been considered to be the isomeric 1-(2-methyl-3-indolyl)-1-(2-methyl-3-indol-eninylidene)ethane (VI).

The structural identification of our compound rests on the following evidence. It forms colourless crystals, which give deep red salts with acids, and also dissolve in concentrated ethanolic potassium hydroxide to give a deep red solution. When, however, the deep red solution in ethanolic hydrogen chloride was made just alkaline, or the solution in concentrated potassium hydroxide was diluted, the initial pale yellow precipitate changed spontaneously to colourless crystals of the original compound: this change also occurred if the yellow crystals were collected, dried, and recrystallised from benzene. It is suggested that the compound (IV; R = H, R′ = Me) when treated with acids gives the cation (IV*A*) and with concentrated alkalis the anion (IV*B*) (cf. König, *Z. angew. Chem.*, 1925, **38**, 747). Both these ions would be deeply (and similarly) coloured by resonance: the cation (IV*A*) is of course similar in type to that found in many cyanine dyes, *e.g.*, the "rosindoles" of Fischer and Wagner (*Ber.*, 1887, **20**, 815) and later workers. It would be

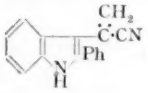


expected that the salts of the cation (IV*A*) would be more stable than those of the anion (IV*B*): hence when solutions of the former are neutralised, or those of the latter diluted with water, the precipitation occurs of the unstable yellow parent compound (VI), which then reverts to the colourless (IV; R = H, R′ = Me), the greater stability of which is due to its more highly aromatic structure. It may be urged that these colour changes are not decisive indications of structure, since the compound (VI) would also give the cation (IV*A*) and the anion (IV*B*) with acids and bases respectively. The structure (VI) would however undoubtedly cause this neutral compound itself to be coloured: compare, for example, the parent compound (2-methyl-3-indolyl)(2-methyl-3-

indoleninylidene)methane which Ellinger and Flamand (*Z. physiol. Chem.*, 1911, **71**, 7) and König (*J. pr. Chem.*, 1911, **84**, 194) describe as a bright yellow compound giving red salts with acids; also the orange-red (XI; R = H, R′ = Me) and the deep mauve (XI; R = H, R′ = Ph) (p. 597) which are also of unambiguous structure. It is highly probable therefore that the compound prepared by Angeli and Marchetti and by Borsche and Groth is (IV; R = H, R′ = Me). Unfortunately, the spectroscopic evidence is indecisive: our compound shows a band at 11·25 μ in harmony with the presence of a $>C{:}CH_2$ group, but the corresponding band in the region of 6 μ which this group should show is not apparent.*

The ethylene (IV; R = H, R′ = Me) underwent ready catalytic hydrogenation to the colourless 1 : 1-di-(2-methyl-3-indolyl)ethane (V; R = H, R′ = Me) which Fischer (*Annalen*, 1887, **242**, 372) prepared by the interaction of paraldehyde and 2-methylindole in the presence of zinc chloride. This reduction does not of course distinguish between (IV; R = H, R′ = Me) and (VI).

2-Phenylindole differed from all other indoles investigated in that its reaction with acetyl cyanide did not give a compound of type (II): its apparently abnormal reaction will therefore be discussed at this stage. Equimolecular quantities of the indole and of acetyl cyanide in pure chloroform solution did not interact at room temperature even during 19 days: when the solution was treated with an excess of hydrogen chloride a tar was formed. When however the solution at room temperature was treated with a small quantity of hydrogen chloride, reaction occurred with the formation of the golden-yellow crystalline α-(2-phenyl-3-indolyl)acrylonitrile (VII). The constitution of this compound, which is apparently the first known indole derivative of acrylonitrile, is based on the following evidence. (*a*) Analysis and molecular-weight determinations. (*b*) The compound has no basic properties and is unaffected by cold dilute aqueous or ethanolic hydrogen chloride. (*c*) Its infra-red absorption spectrum shows bands at 3·01, 4·51, and 14·27 μ, corresponding to the −NH−, −CN, and −Ph groups respectively, but that corresponding to the $>C{:}CH_2$ group is rendered uncertain by the phenyl group. (*d*) The compound underwent hydrolysis when its solution in cold concentrated sulphuric acid was poured on ice, with the formation of yellow crystals of α-(2-phenyl-3-indolyl)acrylamide (VIII). The spectrum of this compound showed bands at 2·9, 3·07, and 3·2 μ, due to the −NH− groups, at 14·44 and 13·47 μ due to phenyl and *o*-phenylene groups respectively, and at 5·97 μ due to $>CO$ present as an acid amide group. (*e*) The compound when boiled with ethanolic potassium hydroxide gave (in small yield) 3-acetyl-2-phenylindole (III; R = H, R′ = Ph), previously prepared by Borsche and Groth (*loc. cit.*) by the interaction of acetic anhydride and 2-phenylindole.

(VII)  (VIII)

1-Methyl-2-phenylindole (I; R = Me, R′ = Ph), which is almost insoluble in chloroform, and acetyl cyanide in ether containing hydrogen chloride gave the colourless 1-cyano-1 : 1-di-(1-methyl-2-phenyl-3-indolyl)ethane (II; R = Me, R′ = Ph) which was unaffected by cold hydrochloric acid, but when heated with soda-lime gave 1 : 1-di-(1-methyl-2-phenyl-3-indolyl)ethylene (IV; R = Me, R′ = Ph). This colourless compound gave a deep red solution in ethanolic hydrogen chloride, but the addition of an excess of ammonia to this solution immediately reprecipitated the unchanged ethylene. It should be noted that the constitution of (IV; R = Me, R′ = Ph) is not in doubt, for an isomeric form comparable to (VI) is now not possible; furthermore, the constitution allocated to the anion (IV*B*) now receives indirect support, for the compound (IV; R = Me, R′ = Ph) could not form an anion of this type, and the compound did not in fact give a red solution in potassium hydroxide solution.

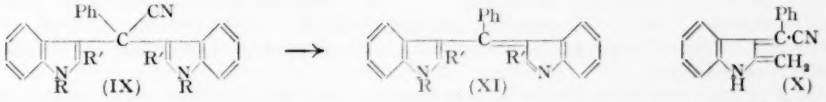
* After this paper was prepared for publication, Saxton (*J.*, 1952, 3592) has briefly discussed the colourless compound which is either (IV; R = R′ = H) or the tautomeric form corresponding to (VI), and considers that the available evidence gives greater support to the latter structure.

Unexpectedly, it was found that the compound (II; R = Me, R′ = Ph) when boiled with ethanolic potassium hydroxide did not lose hydrogen cyanide, but underwent hydrolysis of the cyano-group followed by decarboxylation, with the formation of the colourless 1 : 1-di-(1-methyl-2-phenyl-3-indolyl)ethane (V; R = Me, R′ = Ph), which was unaffected by hydrochloric acid.

1 : 2-Diphenylindole and acetyl cyanide similarly gave 1-cyano-1 : 1-di-(1 : 2-diphenyl-3-indolyl)ethane (II; R = R′ = Ph), together however with a compound the composition of which indicated that it was α-(1 : 2-diphenyl-3-indolyl)acrylonitrile, but the quantity available was too small for decisive identification. The compound (II; R = R′ = Ph) when heated with soda-lime gave the colourless 1 : 1-di-(1 : 2-diphenyl-3-indolyl)ethylene (IV; R = R′ = Ph) which dissolved in concentrated ethanolic hydrogen chloride to give a deep purplish-red colour which was almost completely discharged by dilution with ethanol; this dissociation of the hydrochloride is not unexpected, however, because the nitrogen atoms in (IV; R = R′ = Ph) would be more feebly basic than those carrying hydrogen or alkyl groups in the previous analogous compounds. The compound (II; R = R′ = Ph) was apparently unaffected by boiling ethanolic potassium hydroxide, in which however it was only slightly soluble.

The products obtained by the action of benzoyl cyanide on 2-methylindole depended markedly on the conditions, as in the case of acetyl cyanide. The indole reacted with benzoyl cyanide in cold chloroform containing a low concentration of hydrogen chloride to give the colourless αα-di-(2-methyl-3-indolyl)benzyl cyanide (IX; R = H, R′ = Me). A higher concentration of hydrogen chloride also led to this compound predominantly, together with a crystalline compound of composition $C_{17}H_{12}N_2$, the spectrum of which showed that it contained the –NH– and –CN groups: this may therefore be α-(2-methylene-3-indolinylidene)benzyl cyanide (X), but the minute yield precluded further investigation. When a chloroform solution of the indole and of benzoyl cyanide was treated with a trace of pyridine and then boiled, only 3-benzoyl-2-methylindole was isolated: Oddo (*Gazzetta*, 1913, **43**, II, 190) has prepared this compound by the action of benzoyl chloride on magnesio-2-methylindole, and Seka (*Ber.*, 1923, **56**, 2058) by subjecting benzonitrile and 2-methylindole to the Hoesch reaction.

The presence of the phenyl group in the compound (IX; R = H, R′ = Me) clearly prevents any reaction of the type (II) ⟶ (IV) when the compound is heated with soda-lime or ethanolic potassium hydroxide; experiment showed that in these circumstances hydrogen cyanide was lost with the formation of orange-red crystalline α-(2-methyl-3-indolyl)-α-(2-methyl-3-indoleninylidene)toluene (XI; R = H, R′ = Me). This compound is identical with that obtained by Fischer and Wagner (*loc. cit.*) by the action of benzoyl chloride on 2-methylindole. It forms fuchsin-red salts with acids, and also when potassium hydroxide is added to its ethanolic solution, in harmony with the mechanism already discussed (p. 595).



2-Phenylindole did not react with benzoyl cyanide in pure chloroform, but in the presence of hydrogen chloride gave the colourless crystalline αα-di-(2-phenyl-3-indolyl)-benzyl cyanide (IX; R = H, R′ = Ph) which in boiling ethanolic potassium hydroxide similarly furnished α-(2-phenyl-3-indolyl)-α-(2-phenyl-3-indoleninylidene)toluene (XI; R = H, R′ = Ph): this compound formed deep mauve crystals, which gave a bluish-black hydrochloride.

1-Methyl-2-phenylindole and 1 : 2-diphenylindole reacted with benzoyl cyanide in the presence of hydrogen chloride to form the colourless αα-di-(1-methyl-2-phenyl-3-indolyl)-benzyl cyanide and the 1 : 2-diphenyl analogue (IX; R = Me, R′ = Ph; and R = R′ = Ph), respectively. These compounds were unaffected by boiling ethanolic potassium hydroxide, in which however they were only very slightly soluble: the quantities available were insufficient adequately to investigate their reaction with soda-lime.

Although the reactivity of the indoles investigated clearly varied with the nature of the substituents, the following generalisations may be made. (*a*) The interaction of acyl cyanides and indoles is strongly catalysed by a low concentration of hydrogen chloride, which almost invariably caused the cyanides to react as if they were ketones, *i.e.*, to give condensation compounds of type (II) and (IX). (*b*) In weakly basic solution, the cyanides act as acylating agents, giving 3-acylindoles of type (III). (*c*) Even in the presence of a high concentration of hydrogen chloride, the Hoesch reaction, by which the ·CO·COR group should have entered the 3-position of the indole, was never encountered, although the potential presence of such compounds was constantly sought throughout the investigation. It is noteworthy that acetyl and propionyl cyanides with resorcinol give diketones of type $(HO)_2C_6H_3$·CO·COR (Borsche and Diacont, *Ber.*, 1930, **63**, 2740), whilst benzoyl and substituted benzoyl cyanides give polyhydroxy-lactones (Borsche and Walter, *Ber.*, 1926, **59**, 461; Borsche, Walter, and Niemann, *Ber.*, 1929, **62**, 1360). The failure of acyl cyanides to give diketones with indoles may be partly due to the fact that under the most favourable conditions for a Hoesch synthesis, *i.e.*, a high concentration of hydrogen chloride, the reaction often becomes too vigorous, with the production of tars.

Experimental

Many of the compounds obtained in this investigation, particularly those of type (II), (IV), (IX), and (XI), tended to give low and inconsistent analytical values for carbon, a feature which Fischer and Wagner (*loc. cit.*) have already noted. This trouble could usually be obviated by thorough removal of traces of tenaciously occluded solvent, followed by particularly careful analysis.

Acetyl and benzoyl cyanide were freshly prepared and redistilled before use. Pure chloroform was used for the condensations.

Acetyl Cyanide and 2-Methylindole.—(*a*) A solution of the indole (1·3 g.) in chloroform (10 c.c.) was diluted with acetyl cyanide (0·75 c.c., 1·05 mol.) and set aside for 24 hours. The crystalline 1-*cyano*-1 : 1-*di*-(2-*methyl*-3-*indolyl*)*ethane* (II; R = H, R′ = Me) (0·9 g., 57%) which had separated was then recrystallised from acetone, giving colourless crystals, m. p. 225—230° (decomp., effervescence) (Found: C, 80·2; H, 6·2; N, 13·6. $C_{21}H_{19}N_3$ requires C, 80·5; H, 6·1; N, 13·4%). Evaporation of the chloroform mother-liquor gave a reddish residue which crystallised when triturated with ethanol; recrystallisation from benzene gave white needles of 3-acetyl-2-methylindole (III; R = H, R = Me), m. p. 200—201°, unchanged by admixture with an authentic sample (Fischer and Pistor, *Ber.*, 1923, **56**, 2318—the action of methyl cyanide and hydrogen chloride on 2-methylindole. They give m. p. 195°; Seka, *loc. cit.*, gives 195—196°).

(*b*) The above solution of reactants was boiled under reflux for 40 minutes. On cooling it deposited the cyano-ethane (1 g., 74%), and the chloroform filtrate on concentration deposited a second crop (0·3 g.).

(*c*) Acetyl cyanide (3 c.c.) and chloroform saturated with hydrogen chloride (5 c.c.) were added in turn to a solution of the indole (5·2 g.) in chloroform (50 c.c.). After 24 hours, the cyano-ethane (5·1 g., 80%) was collected and recrystallised as before (Found: C, 80·6; H, 6·0; N, 13·55%). Concentration of the chloroform gave a small second crop, but the acetylindole could not be detected.

(*d*) A mixture similar to that in (*c*) was boiled under reflux for 30 minutes, during which a copious deposit of the cyano-ethane (5·6 g., 89%) was formed (Found: C, 80·1; H, 6·0%). Again, no acetylindole could be detected.

(*e*) When a slow stream of hydrogen chloride was passed into a solution of the indole and acetyl cyanide, prepared as in (*a*), a tar resulted. No crystalline material could be obtained from this product either directly or after attempted hydrolysis, and no diketone or keto-ketimine had apparently been formed. The chloroform solution which had been decanted from the tar gave a trace of the cyano-ethane.

1 : 1-(*Di*-2-*methyl*-3-*indolyl*)*ethylene* (IV; R = H, R′ = Me).—(*a*) An intimate powdered mixture of the cyano-ethane (1 g.) and soda-lime (2 g.) was heated in a tube, sloping slightly downwards towards the mouth, at 200° rising to 260° at 3 mm. Two layers of sublimate could readily be distinguished. One consisted of 2-methylindole (0·04 g.), identified by mixed m. p. and by its picrate, m. p. 136—137°. The second consisted of yellowish crystals, m. p. 196—200° (0·75 g.), which after repeated recrystallisation from benzene gave the colourless

ethylene (IV; R = H, R′ = Me), m. p. 201—203° (Found : C, 84·0; H, 6·3; N, 9·9. $C_{20}H_{18}N_2$ requires C, 83·85; H, 6·3; N, 9·8%).

(*b*) When the pure cyano-ethane was heated alone, similar results were obtained; a sodium hydroxide trap, placed between the tube and the pump, subsequently contained sodium cyanide, indicating the evolution of hydrogen cyanide.

(*c*) A solution of the cyano-ethane (1 g.) in aqueous-ethanolic 10% potassium hydroxide (20 c.c.) was boiled under reflux for 10 hours. The dark red solution on dilution with water gave an amorphous yellow precipitate which when set aside hardened to the colourless crude ethylene, m. p. 188—190° (0·8 g.), increased by recrystallisation from benzene to 200—202° (Found : C, 84·5; H, 6·4; N, 9·5%). This is the most convenient method of preparing the indolyl-ethylene from the cyano-ethane.

(*d*) 2-Methylindole (1·3 g.), ethyl orthoacetate (0·8 g.), concentrated hydrochloric acid (0·1 c.c.), and zinc chloride (a trace) were heated on a water-bath for 3 hours. The dark red product was extracted with boiling light petroleum (b. p. 60—80°), and the residue dissolved in ethanol and then run into dilute aqueous ammonia. The yellow precipitate when recrystallised as before gave the colourless indolyl-ethylene, m. p. 195—200°, in low yield. This method was based on König's similar preparation (*loc. cit.*) of the lower homologue by the interaction of 2-methylindole and ethyl orthoformate in the presence of acid.

(*e*) Borsche and Groth's preparation (*loc. cit.*) by the interaction of acetyl chloride and 2-methylindole was repeated, and the indolyl-ethylene again obtained as colourless crystals, m. p. 201—203° (Found : C, 83·6; H, 6·8; N, 9·9%).

Our colourless samples of the ethylene (IV; R = H, R′ = Me) slowly became pink on exposure to light and air, which probably explains why Borsche and Groth (*loc. cit.*) describe it as pink.

Hydrochloride. When concentrated hydrochloric acid was carefully added to a concentrated acetone solution of the base, the dark red crystalline hydrochloride was precipitated. It was recrystallised repeatedly from ethanolic hydrogen chloride, but its m. p. remained indefinite and its analyses inconsistent, probably owing to instability, as it readily became brown on exposure to air.

Sulphate. This was similarly prepared, and recrystallised from ethanol, forming dark red crystals, decomp. 236°.

Oxalate. When a concentrated acetone solution of the ethylene and oxalic acid was warmed and stirred, the *oxalate* separated from the deep red solution, and when recrystallised from ethanol formed reddish-orange crystals, m. p. 160—161° (Found : C, 69·2; H, 5·3; N, 7·6. $C_{20}H_{18}N_2,C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 69·4; H, 5·4; N, 7·4%).

Picrate. This was readily prepared in ethanol, and after recrystallisation from ethanol formed dark red crystals, m. p. 195° (decomp., after preliminary darkening) (Found : C, 61·1; H, 4·2; N, 13·6. $C_{20}H_{18}N_2,C_6H_3O_7N_3$ requires C, 60·6; H, 4·1; N, 13·6%).

Attempted Synthesis of (VI).—Angeli and Marchetti (*loc. cit.*) considered that their synthesis of the supposed (VI) depended on the intermediate formation of 3-acetyl-2-methylindole, which underwent condensation with unchanged 2-methylindole. We have failed to condense these compounds in spite of a wide variety of conditions employed : for example, the 3-acetyl-2-methylindole was recovered unchanged after equimolecular mixtures with 2-methylindole had been treated in ethanol with hydrogen chloride or with sodium ethoxide at various temperatures, and when the mixtures had been heated with zinc chloride, or sulphuric acid, or a solution of phosphoric anhydride in syrupy phosphoric acid. This inertness of the acetyl-indole contrasts sharply with the marked reactivity of indole-3-aldehyde and 2-methylindole-3-aldehyde which condense readily with indoles unsubstituted in the 2- or 3-position (Ellinger and Flamand, *loc. cit.*; König, *loc. cit.*).

2-Methylindole did not react with acetic acid (alone or with hydrochloric acid), although Scholtz (*Ber.*, 1913, **46**, 2138) has shown that it reacts readily with formic acid to give the formate of the orange-yellow lower homologue of (VI).

1 : 1-*Di*-(2-*methyl*-3-*indolyl*)*ethane* (V; R = H, R′ = Me).—A solution of the indolyl-ethylene (IV; R = H, R′ = Me) (2 g.) in ethanol (100 c.c.) was heated with Raney nickel (1 g.), filtered, mixed with more nickel (1 g.), and hydrogenated at room temperature and pressure, one mol. of hydrogen being readily absorbed. Filtration and concentration gave the ethane (V; R = H, R′ = Me), colourless crystals (from benzene), m. p. 209—210° (Found : C, 83·3; H, 6·65; N, 9·7. Calc. for $C_{20}H_{20}N_2$: C, 83·3; H, 7·0; N, 9·7%). Fischer (*loc. cit.*) gives m. p. 191°, but a sample prepared by his method had m. p. 209—210°, unchanged by admixture with the above sample.

Acetyl Cyanide and 2-Phenylindole.—Chloroform (60 c.c.) which had been saturated with hydrogen chloride was added to a solution of 2-phenylindole (5·8 g.) and acetyl cyanide (4·2 c.c., 2 mols.) in chloroform (120 c.c.), and the mixture set aside for 4 days. After filtration to remove a trace of tar, the solvent was evaporated and the red viscous residue rubbed with ethanol. The pale yellow microcrystalline powder (4·1 g.; m. p. 170—172°) thus obtained, when repeatedly recrystallised from ethanol, gave golden-yellow crystals of α-(*2-phenyl-3-indolyl*)*acrylonitrile* (VII), m. p. 174—175·5° (Found: C, 83·4; H, 4·75; N, 11·55%; *M*, ebullioscopic in ethanol, 229. $C_{17}H_{12}N_2$ requires C, 83·6; H, 4·95; N, 11·5%; *M*, 244).

Hydrolysis. (*a*) A solution of the nitrile (VII) in cold sulphuric acid was set aside for 24 hours and then added with stirring to ice-water. The precipitate, when repeatedly recrystallised from ethanol, gave α-(*2-phenyl-3-indolyl*)*acrylamide* (VIII) as yellow crystals, m. p. 203—205° (Found: C, 77·75; H, 5·6; N, 10·6. $C_{17}H_{14}ON_2$ requires C, 77·8; H, 5·4; N, 10·7%).

(*b*) Aqueous-ethanolic 10% potassium hydroxide (20 c.c.) was added to a solution of the nitrile (VII) (1 g.) in boiling ethanol (40 c.c.) which was boiled under reflux for 1 hour, and the dark red solution was then run into dilute acetic acid. The impure yellow precipitate, m. p. 80—135°, on recrystallisation from ethanol furnished 1-acetyl-2-phenylindole, m. p. 220—221° (0·01 g.) (Found: C, 81·7; H, 5·9; N, 6·1. Calc. for $C_{16}H_{13}ON$: C, 81·7; H, 5·6; N, 6·0%). A sample prepared by the method of Borsche and Groth (*loc. cit.*) also had m. p. 220—221°, alone and mixed. No other pure compound could be isolated from the original ethanolic solution.

When a mixture of the nitrile (VII) and soda-lime was heated under pressure, only 2-phenylindole could be isolated from sublimate obtained.

Attempts to prepare the cyanohydrin of 3-acetyl-2-phenylindole were unsuccessful: otherwise, dehydration of this cyanohydrin might have afforded a ready synthesis of the nitrile (VII).

Acetyl Cyanide and 1-Methyl-2-phenylindole (I; R = Me, R′ = Ph).—A solution of the indole (4·14 g.) and acetyl cyanide (1·42 c.c., 1 mol.) in absolute ether (80 c.c.) was saturated with hydrogen chloride and set aside for 24 hours. After filtration from a trace of dark material, and evaporation, the residue was stirred with warm methanol. The colourless solid thus deposited gave, on recrystallisation from benzene, 1-*cyano*-1 : 1-*di*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethane* (II; R = Me, R′ = Ph), m. p. 237—238° (Found: C, 85·1; H, 6·0; N, 9·1. $C_{33}H_{27}N_3$ requires C, 85·1; H, 5·85; N, 9·0%).

An intimate mixture of the cyano-ethane (1 g.) and soda-lime (2·5 g.) was placed in a sublimation tube, covered with more soda-lime (2·5 g.), and heated at 240—270°/0·5 mm. The main sublimate consisted of colourless plates, which when recrystallised from *cyclo*hexane gave 1 : 1-*di*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethylene* (IV; R = Me, R′ = Ph), m. p. 193—194° (Found: C, 87·6; H, 6·1; N, 6·5. $C_{32}H_{26}N_2$ requires C, 87·6; H, 6·0; N, 6·4%). This compound gave a deep red solution in ethanolic hydrogen chloride, which, however, when poured into an excess of aqueous ammonia, deposited the colourless crystalline ethylene.

A mixture of the cyano-ethane (0·5 g.) and aqueous ethanolic 10% potassium hydroxide (10 c.c.) was diluted with ethanol (20 c.c.) and boiled under reflux for 5 hours, the clear solution slowly becoming turbid. After cooling, the crystalline precipitate, m. p. 210—215°, was recrystallised from aqueous acetone, affording 1 : 1-*di*-(1-*methyl*-2-*phenyl*-3-*indolyl*)*ethane* (V; R = Me, R′ = Ph), m. p. 212—215° (Found: C, 87·7; H, 6·25; N, 6·1. $C_{32}H_{28}N_2$ requires C, 87·2; H, 6·4; N, 6·4%). This compound remained colourless when treated with hydrochloric acid.

Alternatively, a solution of the cyano-ethane in 70% sulphuric acid was heated until the colour had changed to orange, then red and finally brown, whereupon the solution was chilled and diluted with water. The brown precipitate, when collected and warmed with ethanol, deposited the above ethane, as very pale yellow crystals, m. p. 210—215°, mixed and unmixed.

Acetyl Cyanide and 1 : 2-Diphenylindole (I; R = R′ = Ph).—A chloroform solution of equimolecular quantities of the indole and the cyanide was saturated with hydrogen chloride, set aside for 48 hours, and filtered, and the chloroform evaporated. The gummy residue was stirred with hot methanol, and the crystalline deposit then quickly filtered from the hot mixture, and washed with more methanol. The deposit, when recrystallised from aqueous acetone, afforded colourless crystals of 1-*cyano*-1 : 1-*di*-(1 : 2-*diphenyl*-3-*indolyl*)*ethane* (II; R = R′ = Ph), m. p. 214—216° (Found: C, 87·9; H, 5·5; N, 7·1. $C_{43}H_{31}N_3$ requires C, 88·0; H, 5·1; N, 6·9%).

The methanolic filtrate and washings on cooling deposited an oil which slowly solidified, and on recrystallisation from methanol gave colourless crystals, m. p. 150°, presumably of α-(1 : 2-

diphenyl-3-indolyl)acrylonitrile (as VII) (Found: C, 86·2; H, 4·8; N, 8·5. $C_{23}H_{16}N_2$ requires C, 86·25; H, 5·0; N, 8·75%).

The cyano-ethane, when heated as before with soda-lime gradually to 300°/0·5 mm., gave a distillate which readily solidified and when recrystallised from ethyl acetate gave colourless 1 : 1-*di*-(1 : 2-*diphenyl-3-indolyl)ethylene* (IV; R = R′ = Ph), m. p. 217·5—219·5° (Found: C, 89·2; H, 5·4; N, 5·1. $C_{42}H_{30}N_2$ requires C, 89·6; H, 5·4; N, 5·0%).

The cyano-ethane was recovered unchanged after a suspension in aqueous-ethanolic 10% potassium hydroxide had been boiled under reflux for 10 hours.

Benzoyl Cyanide and 2-Methylindole.—(*a*) Chloroform (2 c.c.), previously saturated with hydrogen chloride, was added to a solution of the indole (2·6 g.) and the cyanide (1·4 g.) in chloroform (20 c.c.), which was set aside for 5 days. The crystals (3·2 g.) which had separated were washed with chloroform and dissolved in a minimum of hot ethanol: water was added dropwise to the hot filtered solution until crystals appeared. On cooling, there were deposited colourless crystals (2·55 g., 68%) of almost pure αα-*di*-(2-*methyl-3-indolyl)benzyl cyanide* (IX; R = H, R′ = Me), which after crystallisation from aqueous methanol darkened at *ca.* 200°, sintered at 215° and melted at 225° to a red liquid (Found: C, 83·0; H, 5·7; N, 11·4. $C_{26}H_{21}N_3$ requires C, 83·2; H, 5·6; N, 11·2%); this was unaffected by cold hydrochloric acid. A small second crop was isolated from the chloroform filtrate by evaporation, and treatment of the residue with ethanol.

(*b*) The previous experiment was repeated, but with use of chloroform (20 c.c.) saturated with hydrogen chloride. The crystals (2 g.) now collected were apparently a mixture: they were thoroughly triturated with acetone (10 c.c.), collected, and washed again with acetone (5 c.c.). The united acetone filtrates when diluted with water deposited the above crystalline cyanide (1·6 g.), which when heated behaved as before with final melting at 223°. The acetone-insoluble residue appeared to be an unstable hydrochloride; cautious addition of water to its methanolic solution gave colourless chlorine-free crystals (0·1 g.), m. p. 295° (decomp.) after repeated recrystallisation from aqueous acetone. They were apparently α-(2-*methylene-3-indolinylidene)benzyl cyanide* (X) (Found: C, 83·1; H, 5·0; N, 11·5. $C_{17}H_{12}N_2$ requires C, 83·6; H, 5·0; N, 11·5%).

(*c*) A solution of the indole (1·3 g.), benzoyl cyanide (0·7 g.), and pyridine (1 drop) in chloroform (10 c.c.) was boiled under reflux for 2 hours and the solvent then evaporated. The reddish oily residue when stirred with ethanol gave colourless crystals of almost pure 3-benzoyl-2-methylindole, m. p. 185—186° (from methanol) (Found: C, 81·7; H, 5·6. Calc. for $C_{16}H_{13}ON$: C, 81·7; H, 5·55%). Oddo (*loc. cit.*) gives m. p. 181°; Seka (*loc. cit.*) gives 181—182°.

An intimate mixture of the cyanide (IX; R = H, R′ = Me) and soda-lime was heated at 0·5 mm. A colourless sublimate of 2-methylindole, m. p. 60°, soon formed, and at 210—290° an orange distillate was obtained; this solidified, and when crystallised slowly from a minimum of hot ethanol afforded deep red crystals of α-(2-methyl-3-indolyl)-α-(2-methyl-3-indoleninylidene)-toluene (XI; R = H, R = Me) which darkened at *ca.* 230°, sintered at 244°, and melted at 247°.

The same compound was more readily obtained when a solution of the cyanide (1 g.) in aqueous-ethanolic 10% potassium hydroxide (40 c.c.) was boiled under reflux for 15 minutes, and the hot red solution then run into water (*ca.* 160 c.c.). The initial amorphous, orange precipitate became granular and darker when the mixture was warmed and stirred, and was then collected, washed with water, dried (0·95 g.), and recrystallised as before, deep red crystals of almost identical m. p. being obtained.

For identification, this compound was also prepared by the method of Fischer and Wagner (*loc. cit.*) and an identical product obtained. Our product, like that of these authors, when freshly precipitated from a solution of one of its salts was amorphous and orange, and was freely soluble in ethanol and ether. When however the amorphous material was heated with water or immersed in ethanol, it slowly formed reddish-orange crystals, which were much less soluble in ethanol and almost insoluble in ether. Slow crystallisation from ethanol gave the larger deep red crystals. The addition of solid potassium hydroxide to its ethanolic solution gave the same fuchsin-red colour as that of its salts with acids. The compound retains water and ethanol very tenaciously, and satisfactory carbon analyses were not obtained.

Benzoyl Cyanide and 2-Phenylindole.—Chloroform (20 c.c.), previously saturated with hydrogen chloride, was added to a solution of the indole (1·93 g.) and benzoyl cyanide (1·35 g., 1 mol.) in chloroform (40 c.c.), which was set aside for 4 days. The almost colourless crystals (1·8 g.) were then collected and recrystallised from aqueous ethanol, affording αα-*di*-(2-*phenyl-3-*

indolyl)benzyl cyanide (IX; R = H, R′ = Ph) which became red at *ca.* 200° and melted at 240—242° (decomp.) (Found: C, 84·2; H, 5·3; N, 8·2. $C_{36}H_{25}N_3,0{\cdot}75H_2O$ requires C, 84·3; H, 5·2; N, 8·2%). This compound also retains water very tenaciously: the sample analysed had previously been heated at 60°/0·1 mm. over phosphoric anhydride for 18 hours.

A solution of the cyanide in aqueous-ethanolic 10% potassium hydroxide was boiled under reflux for 3 hours, and the bluish-violet solution then filtered into much water. The amorphous red precipitate became crystalline and mauve when the suspension was warmed and stirred. It was insoluble in most solvents, and was recrystallised by adding water cautiously to a hot solution in ethanolic pyridine (1 : 2) until a turbidity was produced; slow cooling gave fine deep mauve crystals of *α-(2-phenyl-3-indolyl)-α-(2-phenyl-3-indoleninylidene)toluene* (XI; R = H, R′ = Ph), m. p. 320—325° to a red liquid (Found: C, 86·6; H, 5·35; N, 6·05. $C_{35}H_{24}N_2,0{\cdot}75H_2O$ requires C, 86·5; H, 5·3; N, 5·8%). A solution in ethanolic pyridine when run slowly into dilute hydrochloric acid deposited the hydrochloride as bluish-black crystals, which sintered at 220° and melted at 235°.

Benzoyl Cyanide and 1-Methyl-2-phenylindole.—Ether (40 c.c.), previously saturated with hydrogen chloride, was added to a solution of the indole (2 g.) and benzoyl cyanide (1·3 g., 1 mol.) in dry ether, and the mixture after 2 days was filtered and evaporated. The grey solid residue was triturated with ethanol, and the product (1·9 g.) on recrystallisation from benzene gave colourless crystals of *αα-di-(1-methyl-2-phenyl-3-indolyl)benzyl cyanide* (IX; R = Me, R′ = Ph), m. p. 289—291° (Found: C, 86·4; H, 5·55; N, 7·65. $C_{38}H_{29}N_3$ requires C, 86·5; H, 5·5; N, 8·0%).

Benzoyl Cyanide and 1 : 2-Diphenylindole.—A solution of the indole (2 g.) and benzoyl cyanide (1·3 g., 1·35 mol.) in dry chloroform (10 c.c.) was saturated with hydrogen chloride, and after 2 days the solvent was evaporated. The residue was stirred with aqueous sodium hydroxide, collected, washed with water, dried (2·2 g.), and recrystallised from benzene, giving colourless *αα-di-(1 : 2-diphenyl-3-indolyl)benzyl cyanide* (IX; R = R′ = Ph), m. p. 303—304° (Found: C, 88·1; H, 4·9; N, 6·3. $C_{48}H_{33}N_3$ requires C, 88·4; H, 5·1; N, 6·45%).

The above three compounds of type (IX) were unaffected by dilute hydrochloric acid.

The ultra-violet absorption spectra of certain of the above compounds, in ethanolic solution, are recorded in the Table (λ in mμ).

(II; R = H, R′ = Me)	$\lambda_{max.}$	290	282	222		$\lambda_{min.}$	287	247	
	ε	14,110	15,000	65,700		ε	12,500	4200	
(II; R = Me, R′ = Ph)	$\lambda_{max.}$	287	223			$\lambda_{min.}$	258	210	
	ε	18,400	73,500			ε	9200	51,200	
(IV; R = H, R′ = Me)	$\lambda_{max.}$	377	280	275	228	$\lambda_{min.}$	337	278	254
	ε	306	19,280	19,350	50,200	ε	188	19,100	11,500
(IV; R = H, R′ = Me) in EtOH containing 2% of N/10-HCl ...	$\lambda_{max.}$	499	350	285	210	$\lambda_{min.}$	410	325	250
	ε	18,900	1780	17,600	38,100	ε	1080	1400	10,500
(V; R = H, R′ = Me)	$\lambda_{max.}$	291	284	227		$\lambda_{min.}$	289	251	203
	ε	12,360	13,100	58,500		ε	11,700	4200	32,000
(VII)	$\lambda_{max.}$	296	220			$\lambda_{min.}$	256	212	
	ε	16,790	26,350			ε	7076	25,370	

It is noteworthy that König (*loc. cit.*) has recorded that (2-methyl-3-indolyl)(2-methyl-3-indoleninylidene)methane, *i.e.*, the lower homologue of (VI), gives a perchlorate having in ethanolic solution $\lambda_{max.}$ 4820, 3500, and 2900, and a sodium salt having similarly $\lambda_{max.}$ 4820, 3700, and 3000. These red salts must presumably give rise to ions analogous to (IV*A*) and (IV*B*) respectively, and their spectra confirm their closely similar structure.

We are greatly indebted to Dr. R. N. Haszeldine for the spectroscopic investigation, to the Government of Singapore for the award of a Queen's Fellowship (K. A. K.), and to Imperial Chemical Industries Limited, Dyestuffs Division, for the gift of various intermediate compounds.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 23rd,* 1952.]

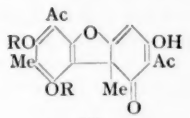
122. *Some Observations on the Constitution of Usnic Acid.*

By D. H. R. Barton and T. Bruun.

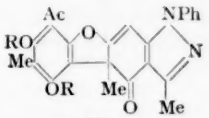
Ozonolysis of usnic acid anhydrophenylhydrazone diacetate affords 3-methyl-1-phenylpyrazole-4 : 5-dicarboxylic acid and a compound $(C_{16}H_{15}O_7)_2$. The latter results from the oxidative coupling of the intermediate 4 : 6-diacetoxy-7-acetyl-5-methylcoumaran-2-one; it is also produced by the oxidation of usnic acid diacetate with potassium permanganate. The degradation of usnic acid anhydrophenylhydrazone by potassium hydroxide in methanol and ethanol is reported. The significance of these results is assessed in terms of Robertson's usnic acid formula.

A number of constitutional formulæ has been suggested for the lichen constituent usnic acid (Dean, *Science Progr.*, 1952, **40**, 635; Mayer and Cook, " Natural Colouring Matters," Reinhold Publ. Corp., 1943, p. 157). Of these (I; R = H) was first proposed by Curd and Robertson (*J.*, 1937, 894). The experiments described in the present paper were designed to test this expression further.

Usnic acid readily affords an anhydrophenylhydrazone (II; R = H), converted by further treatment with phenylhydrazine into the phenylhydrazone anhydrophenylhydrazone (III) (Asahina and Yanagita, *Ber.*, 1938, **71**, 2260). The residual ketonic oxygen in this compound and its equivalent trifunctional derivatives has not hitherto been characterised and it could, *a priori*, be ketonic, oxidic, or ethereal. An attempt to prepare an oxime from (III) proved abortive, the product being the oxime anhydrophenylhydrazone (IV). The latter was also obtained, with concomitant deacetylation, when the anhydrophenylhydrazone diacetate (II; R = Ac) was treated with hydroxylamine hydrochloride in pyridine. Such steric resistance to oximation is not incompatible with structure (III), and indeed the infra-red spectrum showed an intense carbonyl band at 1673 cm.$^{-1}$ ($CHCl_3$ solution) indicative of an unsaturated ketonic function (in a six-membered ring).



(I)



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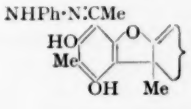

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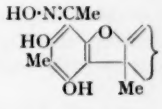
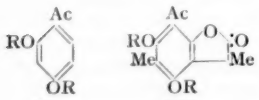


(IV)

The presence of a benzenoid ring in usnic acid was verified in two ways. First, conversion of usnic acid anhydrophenylhydrazone, which shows absorption of relatively low intensity above 300 mμ in the ultra-violet, into the phenylhydrazone anhydrophenylhydrazone (III) produces a characteristic band at 333 mμ of high intensity ($\varepsilon = 25{,}500$). A comparable marked change of absorption spectrum is produced when resacetophenone (V; R = H) is converted into its phenylhydrazone, the latter showing a band at 337 mμ ($\varepsilon = 25{,}500$). Similar arguments in favour of the presence of a system of resacetophenone type, based on ultra-violet measurements, have been adduced by MacKenzie (*J. Amer. Chem. Soc.*, 1952, **74**, 4067). Secondly, the anhydrophenylhydrazone diacetate showed a band at 1783 cm.$^{-1}$ (CCl_4 solution) in the infra-red, characteristic of a phenolic acetate, and of an intensity (cf. Jones, Ramsay, Keir, and Dobriner, *ibid.*, p. 80) corresponding to two such chromophores. Resacetophenone diacetate (V; R = Ac) similarly showed phenolic acetate bands at 1760 and 1775 cm.$^{-1}$ ($CHCl_3$ solution).

Ozonolysis of usnic acid diacetate by Schöpf and Ross (*Annalen*, 1941, **546**, 1; cf. Asahina and Okasaki, *J. Pharm. Soc. Japan*, 1943, **63**, 618) provided strong support for the Robertson formula. They isolated a product, m. p. 130—131°, formulated as 4 : 6-diacetoxy-7-acetyl-3 : 5-dimethylcoumaran-2-one (VI; R = Ac), and 2 : 4-diketopentanoic acid (VII); these account for all but one of the carbon atoms of usnic acid. It seemed to us, however, that there was no definitive evidence that (VII) was formed from (VIII), and indeed that there was only meagre support for the location of the carbon atom lost on ozonolysis within the usnic acid structure (I; R = H). We therefore ozonised usnic acid

anhydrophenylhydrazone diacetate (II; R = Ac). The acid fraction gave 3-methyl-1-phenylpyrazole-4 : 5-dicarboxylic acid (IX), the identity of which was confirmed by thermal decarboxylation to 3-methyl-1-phenylpyrazole-4-carboxylic acid (X). The dicarboxylic acid (X) retains the carbon atom " lost " in the previous ozonolysis, and substantiates its attachment in (I; R = H).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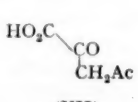
(VI)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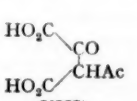
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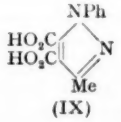
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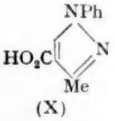
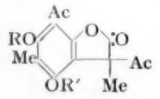
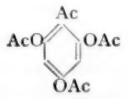
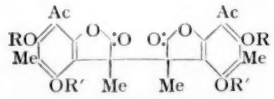

(X)

The neutral fraction from the ozonolysis afforded a compound, m. p. 225—226°, identical with a substance obtained by Takahashi and Shibata (*J. Pharm. Soc. Japan*, 1951, **71**, 1083) by oxidation of usnic acid diacetate with potassium permanganate. These authors had assigned to it the molecular formula $C_{18}H_{18}O_8$ and had regarded it as 4 : 6-diacetoxy-3 : 7-diacetyl-3 : 5-dimethylcoumaran-2-one (XI; R = R′ = Ac). Such a structure for our neutral ozonolysis product would imply that usnic acid had two more carbon atoms than the previously accepted molecular formula, $C_{18}H_{16}O_7$. A search of the earlier usnic acid literature revealed little justification for such a revision and, indeed, a precision molecular-weight determination on usnic acid diacetate gave a value in close agreement with the previously accepted theoretical value. The ozonolysis of usnic acid diacetate was therefore reinvestigated. The neutral fraction gave a compound, m. p. 131—132°, in agreement with previous workers. The constitution (VI; R = Ac) of this substance was confirmed in two ways. First, a precise molecular-weight determination gave a value in excellent agreement with the formula $C_{16}H_{16}O_7$. Secondly, the infra-red spectrum (in $CHCl_3$) showed bands at 1822 (γ-lactone with vinylic conjugation), 1780 (phenolic acetate; intensity corresponding to two acetate residues), and 1698 cm.$^{-1}$. The last band is due to an acetyl group attached to a benzene ring, as in resacetophenone diacetate (V; R = Ac), which shows a carbonyl band at 1690 cm.$^{-1}$ (in $CHCl_3$). The infra-red spectrum of the ozonolysis fragment, m. p. 225—226°, was practically identical with that of (VI; R = Ac), showing, therefore, the presence of identical carbonyl functions. The ultra-violet absorption spectra were also almost identical.


(XI)

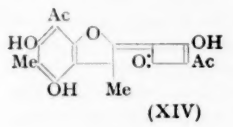

(XII)


(XIII)

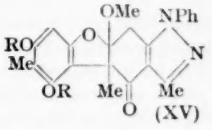
The nature of the compound, m. p. 225—226°, was finally established by its formation in good yield from (VI; R = Ac) by potassium permanganate or ozonolysis. Clearly it is produced by oxidative coupling and has the molecular formula $(C_{16}H_{15}O_7)_2$. A molecular-weight determination supported this conclusion. The analytical data of Takahashi Shibata (*loc. cit.*) are, in fact, in better agreement with the formula $(C_{16}H_{15}O_7)_2$ than with $C_{18}H_{18}O_8$. In so far as phloracetophenone triacetate (XII) shows no tendency to undergo oxidative coupling on treatment with potassium permanganate, and in view of the almost identical infra-red and ultra-violet spectra, with regard to both wave-length and intensity, of (VI; R = Ac) and the compound $(C_{16}H_{15}O_7)_2$, we formulate the latter as (XIII; R = R′ = Ac). There is good analogy for the postulated oxidative coupling (Bernatek and Berner, *Acta Chem. Scand.*, 1949, **3**, 1117).

In reviewing the chemistry of usnic acid as elucidated in this and earlier work it seemed to us that there was at least one other formula (XIV) which, with suitable assumptions, would explain the majority of the facts and would, in addition, afford an acceptable mechanistic explanation for its ready racemisation. In order to differentiate between (I; R = H) and (XIV), the degradation of usnic acid anhydrophenylhydrazone by potassium hydroxide was studied. In methanol this furnished a methoxy-compound, $C_{23}H_{22}O_5N_2$, which on the basis of (II; R = H) should be (XV; R = H). In agreement it afforded a

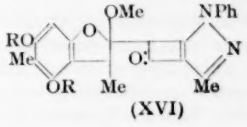
diacetate which showed bands in the infra-red at 1770 (phenol acetate) and at 1672 cm.$^{-1}$ [the sterically hindered ketone group (see above) of the parent anhydrophenylhydrazone], was stable to ozone and, on attempted oximation, gave back the parent phenol. The presence in the phenol of a free aromatic position *ortho* to a hydroxyl group was shown by its ready coupling with diazotised anthranilic acid—usnic acid anhydrophenylhydrazone does not, of course, couple readily with diazonium salts. On the basis of (XIV) the methanolic potassium hydroxide degradation product would be (XVI; R = H). The main objection to this comes from the infra-red spectrum (see above) of the diacetate. *cyclo*Butanones have carbonyl maxima near 1780 cm.$^{-1}$. Conjugation would reduce the frequency of the band, but it would be most unexpected if it were to be reduced to 1672 cm.$^{-1}$ or if the frequency should remain unchanged on going from usnic acid phenylhydrazone anhydrophenylhydrazone (see above) to (XVI; R = Ac).



(XIV)

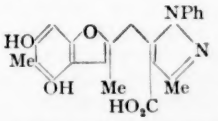


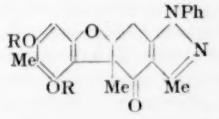
(XV)



(XVI)

(XVII)





(XVIII)

Degradation of usnic acid anhydrophenylhydrazone under more vigorous conditions, with aqueous or (better) ethanolic potassium hydroxide, afforded a high-melting, optically inactive acid, $C_{22}H_{20}O_5N_2$, further characterised as the diacetate methyl ester. The acid coupled at once with diazotised anthranilic acid. This compound may be formulated as (XVII) on the basis of (I; R = H) for usnic acid. It was also obtained in small amount as a by-product in the treatment of the anhydrophenylhydrazone with methanolic potassium hydroxide.

In support of formula (I; R = H) for usnic acid, and against (XIV), dihydrousnic acid diacetate (XVIII; R = Ac) showed bands (in CS_2) at 1780 (phenol acetate), 1690 (acetyl attached to a benzene ring), and 1676 cm.$^{-1}$ (conjugated ketone).

There remains for discussion the mechanism of racemisation of usnic acid. MacKenzie (*loc. cit.*) suggested that this may involve homolysis. It seems to us that this is somewhat improbable, (*a*) because usnic acid anhydrophenylhydrazone is not racemised in boiling xylene solution whereas usnic acid itself is and (*b*) because the racemisation of usnic acid, as in the preparation of racemic usnic acid diacetate from the optically active acid (Asahina and Yanagita, *Ber.*, 1939, **72**, 1140), is acid-catalysed. We conclude that, whilst a plausible mechanism for the racemisation has as yet to be devised, Robertson's structure (I) for usnic acid is probably correct.

Experimental

Unless specified to the contrary rotations were determined in chloroform solution at room temperature (15—25°). Light petroleum refers to the fraction of b. p. 40—60°. Ultra-violet absorption spectra were measured in ethanol solution with a Unicam S.P. 500 Spectrophotometer. Infra-red absorption spectra were kindly determined by Dr. A. R. H. Cole (University of Western Australia) and by Dr. J. E. Page of Messrs. Glaxo Laboratories Ltd. Electrometric titrations were carried out in aqueous solution at room temperature using a Cambridge pH meter; during titrations precautions were taken to prevent ingress of carbon dioxide; a glass electrode was used in the usual way with a calomel cell as reference electrode. Precise molecular weights were kindly determined in benzene solution by Dr. R. C. Mehrotra using a modified Menzies–Wright ebulliometer (Bradley, Mehrotra, and Wardlaw, *J.*, 1952, 2027).

The experiments reported below were carried out with (+)-usnic acid, $[\alpha]_D$ from +445° to +515° (*c*, 2·00 to 3·19) and with (−)-usnic acid, $[\alpha]_D$ −445° to −478° (*c*, 2·00 to 3·08), the rotations varying slightly with the batch of acid supplied.

Usnic Acid Diacetate.—The (+)-diacetate was prepared according to the directions of

Asahina and Yanagita (*Ber.*, 1938, **71**, 2260), care being taken that the temperature did not exceed 50°. Recrystallised from methanol it had m. p. 203—204°, $[\alpha]_D$ +240° (*c*, 2·85), $\lambda_{max.}$ 224 mμ (ε = 26,000), inflexions at 249 and 305 mμ (ε = 17,000 and 9000 respectively) (Found: *M*, 424; Calc. for $C_{22}H_{20}O_9$: *M*, 428). The (−)-diacetate was prepared as for the (+)-compound (see above). It had the same m. p. and $[\alpha]_D$ −235° (*c*, 1·82).

Usnic Acid Anhydrophenylhydrazone (II; R = H).—The (+)-anhydrophenylhydrazone (Asahina and Yanagita, *loc. cit.*; they report m. p. 195°) recrystallised from chloroform–ethanol, had m. p. 199—200°, $[\alpha]_D$ +620° (*c*, 2·13), +624° (*c*, 1·40), $\lambda_{max.}$ 221, 253, 287, and 370 mμ (ε = 37,000, 29,000, 24,000, and 4000 respectively) (Found: C, 68·6; H, 5·05. Calc. for $C_{24}H_{20}O_5N_2$: C, 69·2; H 4·85%). With acetic anhydride in pyridine at room temperature overnight it afforded the *diacetate*, m. p. 225—226° (from methanol containing a little chloroform), $[\alpha]_D$ +426° (*c*, 2·15), $\lambda_{max.}$ 245 and 296 mμ, $\lambda_{inflex.}$ 349 mμ (ε = 34,500, 12,500, and 4000 respectively) (Found: C, 67·4; H, 4·95; N, 5·65, 5·75. $C_{28}H_{24}O_7N_2$ requires C, 67·2; H, 4·85; N, 5·6%).

The anhydrophenylhydrazone diacetate (300 mg.) was refluxed for 6 hours in xylene (25 ml.). The xylene was removed *in vacuo* on the steam-bath and the residue recrystallised from methanol to give unchanged diacetate, identified by m. p., mixed m. p., and $[\alpha]_D$ +411° (*c*, 1·41).

Prepared in analogous ways were (−)-*usnic acid anhydrophenylhydrazone*, m. p. 198—199° $[\alpha]_D$ −604° (*c*, 2·28) (Found: C, 68·6; H, 4·65%), and its *diacetate*, m. p. 222—223°, $[\alpha]_D$ −414° (*c*, 2·12) (Found: C, 67·0; H, 4·35; N, 6·15%).

(+)-*Usnic Acid Phenylhydrazone Anhydrophenylhydrazone* (III).—When prepared according to Widman (*Annalen*, 1900, **310**, 230), this had a wide melting range but was converted in refluxing ethanol into the higher-melting form, m. p. 235—236° (decomp.), $[\alpha]_D$ +512° (*c*, 2·10), $\lambda_{max.}$ 258, 303, and 333 mμ (ε = 33,000, 24,000, and 25,500 respectively). For this compound Asahina and Yanagita (*loc. cit.*) reported m. p. (higher-melting form) 233°, $[\alpha]_D$ +500°.

Treatment of the phenylhydrazone anhydrophenylhydrazone or of the anhydrophenylhydrazone diacetate with excess of hydroxylamine hydrochloride in pyridine on the steam-bath for 1 hour afforded (+)-*usnic acid anhydrophenylhydrazone oxime* (IV), m. p. 279—280° (decomp.) (from chloroform), $[\alpha]_D$ +610° (*c*, 0·48; 2-dm. tube), $\lambda_{max.}$ 223, 257, and 368 mμ (ε = 34,500, 33,500, and 3500 respectively) (Found: N, 9·45. $C_{24}H_{21}O_5N_3$ requires N, 9·75%).

Degradation of Usnic Acid Anhydrophenylhydrazone with Potassium Hydroxide in Methanol.—The anhydrophenylhydrazone (200 mg.) was refluxed with methanolic potassium hydroxide (10 ml. of methanol; 2·0 g. of potassium hydroxide) on the steam-bath for 3 hours. After dilution with water, ether-extraction and working up in the usual way gave the *compound* (XV; R = H). After washing with a little ether and recrystallisation from chloroform–light petroleum the (−)-isomer had m. p. 206—207°, $[\alpha]_D$ −380° (*c*, 0·81), $\lambda_{max.}$ 261 and 326 mμ (ε = 19,500 and 2000 respectively) (Found: C, 67·6; H, 5·4; N, 6·45; OMe, 8·15. $C_{23}H_{22}O_5N_2$ requires C, 67·95; H, 5·45; N, 6·9; OMe, 7·65%). Similarly the (+)-isomer had m. p. 206—207°, $[\alpha]_D$ +376° (*c*, 0·72), $\lambda_{max.}$ 261 and 326 mμ (ε = 18,000 and 2000 respectively) (Found: N, 7·3%). Both isomers coupled readily with diazotised anthranilic acid.

With acetic anhydride in pyridine at room temperature overnight the (−)-isomer gave the *diacetate* (XV; R = Ac). Recrystallised from chloroform–methanol this had m. p. 209—210° (depressed to 170—190° on admixture with starting material), $[\alpha]_D$ −280° (*c*, 2·25), $\lambda_{max.}$ 262 mμ (ε = 17,000) (Found: C, 66·25; H, 5·3; N, 5·8. $C_{27}H_{26}O_7N_2$ requires C, 66·1; H, 5·35; N, 5·7%). Attempted oximation with hydroxylamine hydrochloride in pyridine on the steam-bath for 1·5 hours gave back the parent phenol, m. p. and mixed m. p. 206—207°, $[\alpha]_D$ −380° (*c*, 0·86), $\lambda_{max.}$ 261 and 326 mμ (ε = 19,500 and 2000 respectively). The (−)-diacetate was recovered unchanged on ozonolysis under the conditions applied successfully to usnic acid diacetate and anhydrophenylhydrazone diacetate (see below).

Degradation of Usnic Acid Anhydrophenylhydrazone with Potassium Hydroxide in Water or Ethanol.—The anhydrophenylhydrazone (200 mg.) was heated with water (10 ml.) containing potassium hydroxide (7·5 g.) on the steam-bath for 1 hour in oxygen-free nitrogen. The anhydrophenylhydrazone only partly dissolved. After cooling, dilution with water, acidification with dilute sulphuric acid, and filtration, unchanged starting material (126 mg.), identified by m. p. and mixed m. p., was recovered. The filtrate was extracted with ether and the ethereal layer in turn extracted with 1% aqueous sodium hydrogen carbonate and then with 2% aqueous sodium carbonate. Acidification of these two extracts furnished an *acid* (XVII) (18 and 12 mg. repectively). Recrystallised from chloroform–methanol this had m. p. 306° (decomp.), α 0°, $\lambda_{max.}$ 246, 305, and 352 mμ (ε = 26,500, 12,500, and 4000 respectively) (Found: C, 67·0; H, 4·85; N, 7·2. $C_{22}H_{20}O_5N_2$ requires C, 67·35; H, 5·15; N, 7·15%). From the ethereal extract

(see above) a further 38 mg. of unchanged starting material were recovered (identified by m. p. and mixed m. p.).

The acid (XVII) was prepared in better yield as follows: The anhydrophenylhydrazone (200 mg.) was refluxed with ethanol (10 ml.) containing potassium hydroxide (2·5 g.) for 2 hours. Working up as outlined above gave 150 mg. of the crude acid. The acid, which was obtained from both the (+)- and the (−)-anhydrophenylhydrazone, was also formed in very small amount in the methanolic potassium hydroxide degradations described above. It gave a strongly positive coupling test with diazotised anthranilic acid.

For further characterisation the acid was converted into the *diacetate methyl* ester by acetylation with pyridine–acetic anhydride and methylation of the product with diazomethane. Recrystallised from methanol or acetone the ester had m. p. 157—158°, α 0°, $\lambda_{max.}$ 237 mμ (ε = 30,000), $\lambda_{inflex.}$ 278 and 306 mμ (ε = 8000 and 5000 respectively) (Found: N, 5·55; OMe, 6·75. $C_{27}H_{26}O_7N_2$ requires N, 5·7; OMe, 6·35%).

Ozonolysis of Usnic Acid Anhydrophenylhydrazone Diacetate.—The ozonolyses were carried out on both (+)- and (−)-diacetate with the same results. The diacetate (500 mg.) in carbon tetrachloride (20 ml.) was treated at 0° with ozonised oxygen until the yellow colour of the solution had been discharged. The resulting ozonide was worked up in various ways: (*a*) by addition of ethanol and heating on the steam-bath for 15 minutes, (*b*) by addition of water and either keeping the mixture overnight or refluxing it on the steam-bath for 15 minutes. In all cases the same two crystalline compounds were isolated. After decomposition of the ozonide, 1% aqueous sodium hydrogen carbonate solution was added and the carbon tetrachloride layer extracted. From the neutral fraction (250 mg.) remaining in the carbon tetrachloride the tetra-acetoxy-dilactone (XIII; R = R′ = Ac) was obtained. This was chromatographed over alumina washed with ethyl acetate (see Mancera, Barton, Rosenkranz, and Djerassi, *J.*, 1952, 1025). Elution with benzene gave the dilactone (XIII; R = R′ = Ac) which, after recrystallisation from chloroform–methanol, had m. p. 225—226°, α 0°, $\lambda_{max.}$ 220 and 296 mμ (ε = 19,000 and 2500 respectively) (Found: C, 60·2; H, 4·8%; *M*, 578, not very accurate owing to sparing solubility. Calc. for $C_{32}H_{30}O_{14}$: C, 60·2; H, 4·75%; *M*, 638). Hydrolysis of the tetra-acetate by cold concentrated sulphuric acid (Takahashi and Shibata, *J. Pharm. Soc. Japan*, 1951, **71**, 1083) gave the tetrahydroxy-dilactone (XIII; R = R′ = H); this had m. p. 270—271° (decomp.) (from acetone), α 0°, $\lambda_{max.}$ 240, 286, and 326 mμ (ε = 12,000, 16,000, and 3400 respectively). Re-acetylation gave back the tetra-acetate, identified by m. p., mixed m. p., and ultra-violet spectrum.

The acid fraction from the ozonolysis was isolated by thorough extraction with ether of the acidified sodium hydrogen carbonate solution. It was treated in a little methanol with a concentrated solution of potassium hydroxide in methanol. This precipitated the insoluble potassium salt which was filtered off and washed with methanol. After acidification of the potassium salt, the liberated 3-methyl-1-phenylpyrazole-4 : 5-dicarboxylic acid (IX) was crystallised from ethanol–benzene or ethanol–chloroform. It had m. p. 199—200° (decomp.), α 0°, $\lambda_{max.}$ 255 mμ (ε = 13,000), and behaved as a dicarboxylic acid on electrometric titration: pK_1 = 2·83, pK_2 = 5·89 (Found: Equiv., 123. Calc. for $C_{12}H_{10}O_4N_2$: Equiv., 123). There was no depression in m. p. on admixture with an authentic specimen of 3-methyl-1-phenylpyrazole-4 : 5-dicarboxylic acid, m. p. 202—203° (decomp.), $\lambda_{max.}$ 255 mμ (ε = 11,000), synthesised by Benary's method (*Ber.*, 1910, **43**, 1065) and purified as above.

The acid obtained from the ozonolysis was decarboxylated on melting, to a carboxylic acid (X), m. p. 194—195°, optically inactive, $\lambda_{max.}$ 266 mμ (ε = 21,500). On electrometric titration this behaved as a monobasic acid, pK = 4·58 (Found: Equiv., 200. Calc. for $C_{11}H_{10}O_2N_2$: Equiv., 202). There was no depression in m. p. on admixture with authentic 3-methyl-1-phenylpyrazole-4-carboxylic acid, m. p. 193—194°, $\lambda_{max.}$ 266 mμ (ε = 24,500), prepared by thermal decarboxylation of the authentic 4 : 5-dicarboxylic acid (cf. Benary, *loc. cit.*).

Oxidation of Usnic Acid Diacetate with Potassium Permanganate.—The same results were obtained with (+)- and (−)-usnic acid diacetate. The diacetate (2 g.) in "AnalaR" acetone (100 ml.) was oxidised with potassium permanganate according to Takahashi and Shibata (*loc. cit.*). Recrystallisation of the product from chloroform–methanol or chloroform–acetone afforded the tetra-acetoxy-dilactone (XIII; R = R′ = Ac), m. p. 225—226° (undepressed on admixture with the compound prepared as above), α 0°, $\lambda_{max.}$ 220 and 297 mμ (ε = 17,500 and 2500 respectively). For further comparison this was hydrolysed to the phenol, m. p. 270—271° (decomp.), α 0°, $\lambda_{max.}$ 240, 286, and 325 mμ (ε = 11,500, 15,500, and 3300 respectively), undepressed in m. p. on admixture with the previous sample. Re-acetylation gave back the tetra-acetate (m. p., mixed m. p., and ultra-violet spectrum).

The tetra-acetate obtained by potassium permanganate was further treated with methanolic hydrochloric acid according to the directions of Takahashi and Shibata (*loc. cit.*). The diacetoxy-dilactone (XIII; R = H, R′ = Ac) thus obtained had, after crystallisation from chloroform–methanol, m. p. 194—195°, α 0°, $\lambda_{max.}$ 220, 256, and 336 mμ (ε = 13,000, 12,500, and 3200 respectively.)

Ozonolysis of Usnic Acid Diacetate.—The same results were obtained with (+)- and (−)-usnic acid diacetate. The diacetate (500 mg.) in carbon tetrachloride (20 ml.) at 0° was treated with ozonised oxygen until the yellow colour had been discharged. The ozonide was decomposed by water and either kept overnight or refluxed on the water-bath for 15 minutes. The neutral fraction of the product was recrystallised by Schöpf and Ross's method (*Annalen*, 1941, **546**, 1), to give 4 : 6-diacetoxy-7-acetyl-3 : 5-dimethylcoumaran-2-one (VI; R = Ac), m. p. 130—131°, α 0°, $\lambda_{max.}$ 218 and 297 mμ (ε = 23,000 and 3300 respectively) (Found: *M*, 319. Calc. for $C_{16}H_{16}O_7$: *M*, 320). The mixed m. p. with the tetra-acetoxy-dilactone (XIII; R = R′ = Ac) (m. p. 225—226°) ranged from 130° to 205° even on very slow heating.

Hydrolysis of the diacetate with cold concentrated sulphuric acid (cf. Takahashi and Shibata, *loc. cit.*) afforded 7-acetyl-4 : 6-dihydroxy-3 : 5-dimethylcoumaran-2-one (VI; R = H), m. p. 233—234°, $\lambda_{max.}$ 238, 284, and 332 mμ (ε = 12,000, 18,000, and 3300 respectively). The mixed m. p. with the tetrahydroxy-dilactone (XIII; R = R′ = H) [m. p. 270—271° (decomp.)] ranged from 230° to 263° even on very slow heating.

Oxidation of 4 : 6-*Diacetoxy-7-acetyl-3* : 5-*dimethylcourmaran-2-one with Potassium Permanganate.*—The lactone (120 mg.) and finely powdered potassium permanganate (60 mg.) in "AnalaR" acetone (5 ml.) were shaken for 30 minutes. The excess of oxidant was destroyed by ethanol, and the manganese dioxide removed. The filtrate was concentrated, whereupon the tetra-acetoxy-dilactone crystallised. Recrystallised from chloroform–methanol, this (65 mg.) had m. p. and mixed m. p. 225—226°, $\lambda_{max.}$ 220 and 297 mμ (ε = 19,000 and 2800). The identity was further confirmed by conversion by methanolic hydrochloric acid (Takahashi and Shibata, *loc. cit.*) into the diacetoxy-dilactone (XIII; R = H, R′ = Ac), $\lambda_{max.}$ 220, 254, and 337 mμ (ε = 12,000, 11,000 and 2700), m. p. 194—195° alone or mixed with the material prepared as above.

Ozonolysis of 4 : 6-*Diacetoxy-7-acetyl-3* : 5-*dimethylcoumaran-2-one.*—The lactone (50 mg.) in carbon tetrachloride (5 ml.) was treated with ozonised oxygen for 1 hour at room temperature. Water was then added and the mixture refluxed on the steam-bath for 20 minutes. Working up in the usual way afforded the tetra-acetoxy-dilactone (XII; R = R′ = Ac), m. p. and mixed m. p. 226—227°, $\lambda_{max.}$ 220 and 297 mμ (ε = 18,000 and 2900).

Dihydrousnic Acid Diacetate.—(+)- and (−)-Usnic acid diacetate were hydrogenated according to the directions of Asahina, Yanagita, and Mayeda (*Ber.*, 1937, **70**, 2462). Recrystallised from methanol, (+)-dihydrousnic acid diacetate had m. p. 148—149°, $[\alpha]_D$ +4·5° (*c*, 4·68), $\lambda_{max.}$ 220, 276, and 316 mμ (ε = 29,000, 11,000, and 6100 respectively), $\lambda_{inflex.}$ 239 mμ (ε = 18,000). Hydrolysis with cold concentrated sulphuric acid gave (−)-dihydrousnic acid, m. p. 147—148°, $[\alpha]_D$ −88° (*c*, 2·86), $\lambda_{max.}$ 228, 283, and 336 mμ (ε = 19,000, 25,500, and 3600 respectively). Asahina, Yanagita, and Mayeda (*loc. cit.*) gave m. p. 150°, $[\alpha]_D$ −84°. (−)-Dihydrousnic acid diacetate likewise had m. p. 148—149°, $[\alpha]_D$ −6° (*c*, 4·88), −6° (*c*, 4·64), −6° (*c*, 1·00), and the derived (+)-dihydrousnic acid, m. p. 147—148°, $[\alpha]_D$ +83° (*c*, 2·38), $\lambda_{max.}$ 228, 283, and 336 mμ (ε = 22,000, 26,500, and 3900 respectively).

(+)-Dihydrousnic acid diacetate (100 mg.) in carbon tetrachloride (5 ml.) was treated with ozonised oxygen for 1 hour at room temperature. After addition of water and refluxing on the steam-bath for 15 minutes, the starting material was recovered (m. p. and mixed m. p. 147—148°).

(+)-Dihydrousnic acid diacetate (200 mg.) was unchanged when refluxed in xylene (20 ml.) for 6 hours {m. p. and mixed m. p. 147—148°, $[\alpha]_D$ +3·5° (*c*, 4·64)}.

Miscellaneous Derivatives.—Resacetophenone diacetate had m. p. 38—38·5°, $\lambda_{max.}$ 248 mμ (ε = 13,500). Resacetophenone phenylhydrazone had m. p. 161—162°, $\lambda_{max.}$ 246, 304, and 337 mμ (ε = 15,500, 13,000, and 25,500, respectively). Resacetophenone 4-acetate had m. p. 74—75°, $\lambda_{max.}$ 257 and 318 mμ (ε = 12,000 and 4600). Phloroacetophenone had λ_{max} 228 and 288 mμ (ε = 15,000 and 19,000 respectively). *Phloracetophenone triacetate*, prepared by treating the keto-phenol with pyridine and acetic anhydride overnight at room temperature and, crystallised from chloroform–light petroleum, formed needles, m. p. 58—59°, $\lambda_{max.}$ 239 mμ (ε = 6500) (Found: C, 57·3; H, 4·7. $C_{14}H_{14}O_7$ requires C, 57·15; H, 4·8%); it gave no colour with ferric chloride whereas the compound previously described under the same name (see Beilstein, Vol. VIII, 2nd Suppl. Vol., p. 394) was said to give a colour and have m. p. 90°. Phlor-

acetophenone triacetate was, in part, recovered unchanged when shaken for 30 minutes with its own weight of finely powdered potassium permanganate in " AnalaR " acetone (m. p. and mixed m. p. 58—59°).

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial Assistance. This work was carried out by one of us (T. B.) whilst in receipt of a Research Fellowship from the Norges Teknisk-Naturvitenskapelige Forskningsråd. We cordially thank Professor N. A. Sörensen (Trondheim) and Professor A. Stoll ((Sandoz, A-G., Basel) for making available supplies of (+)- and (−)-usnic acid respectively.

BIRKBECK COLLEGE, LONDON, W.C.1. [*Received, November 7th,* 1952.]

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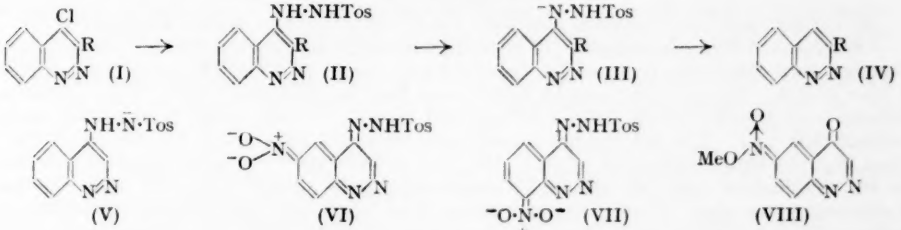
123. *Cinnolines. Part XXX.* The Nature of the* $C_{(3)}$*-Position. The Synthesis of 3-Methyl-, 3-Chloro-, and 3-Bromo-cinnoline; also, of Cinnoline and the* Bz*-Nitrocinnolines.*

By E. J. ALFORD and K. SCHOFIELD.

The cinnolines mentioned in the title have been prepared by treating their 4-chloro-derivatives with toluene-*p*-sulphonylhydrazide, and decomposing the resulting 4-toluene-*p*-sulphonylhydrazinocinnolines with aqueous sodium carbonate.

WE recently described the synthesis of 3-hydroxycinnoline (*J.*, 1952, 2102) as the beginning of work aimed at establishing the character of the cinnoline $C_{(3)}$-position. Three other compounds necessary for this purpose are now described, and we record the preparation by the same method of cinnoline and the *Bz*-nitrocinnolines.

Since Dewar (*J.*, 1944, 619) first used the method in the quinazoline series, several authors (Albert, Brown, and Duewell, *J.*, 1948, 1284; Albert and Royer, *J.*, 1949, 1148; Clinton, *J. Amer. Chem. Soc.*, 1949, **71**, 755; Badger, Seidler, and Thomson, *J.*, 1951, 3207) have removed reactive halogen atoms from heterocyclic compounds by reaction with toluene-*p*-sulphonylhydrazide and decomposition of the product with alkali. Recently Morley (*J.*, 1951, 1971) attempted to use this method to prepare 6-nitrocinnoline, but, although 4-chloro-6-nitrocinnoline reacted readily with the hydrazide, the resulting 6-nitro-4-toluene-*p*-sulphonylhydrazinocinnoline gave none of the desired product when treated with sodium carbonate. In contrast, the corresponding intermediate from 4-chloro-8-methoxycinnoline gave good yields of 8-methoxycinnoline (Alford, Marsh, Irving, and Schofield, *J.*, 1952, 3009), and the method has been applied satisfactorily to a number of 4-chlorocinnolines (I), as is now described.



(Tos = *p*-$C_6H_4Me{\cdot}SO_2$)

Cinnoline itself was readily prepared by this procedure. In small-scale experiments the recovery of (II; R = H) as its hydrochloride, after treatment of 4-chlorocinnoline with two equivalents of toluene-*p*-sulphonylhydrazide in chloroform, was almost quantitative, but was reduced on the larger scale, probably because of the instability of 4-chloro-

* Part XXIX, *J.*, 1952, 3009.

cinnoline. Hot aqueous sodium carbonate converted (II; R = H) into cinnoline in 80% yield. The method represents a practicable synthesis of cinnoline, but is probably not so convenient as that described by Jacobs, Winstein, Henderson, and Spaeth (*J. Amer. Chem. Soc.*, 1946, **68**, 1310; cf. Morley, *loc. cit.*).

Equally satisfactory were the results with 4-chloro-3-methyl-, 3-bromo-4-chloro-, and 3 : 4-dichloro-cinnoline.

Morley (*loc. cit.*) obtained two mononitro-derivatives, m. p. 135—136° and 151—152°, by nitrating cinnoline, and the availability of the 4-chloro-*Bz*-nitrocinnolines (Schofield and Simpson, *J.*, 1945, 512; Schofield and Theobald, *J.*, 1949, 2404) offered a means of orienting these products. The 4-chloro-nitrocinnolines reacted readily with toluene-*p*-sulphonylhydrazide. The crude crystalline products of type (II) underwent characteristic colour changes during crystallisation from acetic acid: the 6-nitro-compound changed from purple to reddish-orange, the 7-nitro-isomer from red to orange, and the 8-nitro-derivative from pink to brownish-red. The pure products proved to be the free bases, and the colour changes may have signified the decomposition of the original crude hydrochlorides. When treated with aqueous ammonia or sodium carbonate the nitro-4-toluene-*p*-sulphonylhydrazinocinnolines produced characteristically coloured solutions (reddish-brown with the 5- and the 7-nitro-compound, purplish-red and intense purple with the 6- and the 8-isomer respectively). The colours are possibly due to anions of the type (III) [which might be tautomeric with (V) (Limpricht, *Ber.*, 1887, **20**, 1238; Albert and Royer, *loc. cit.*)], and the resonance forms (VI) and (VII) would explain the special intensity of those observed with the 6- and the 8-nitro-compound. With warm aqueous sodium carbonate the colours were gradually destroyed, and moderate yields of 7- and 8-nitrocinnoline were obtained. Like Morley (*loc. cit.*) we were unable to isolate even a trace of 6-nitrocinnoline. Although 6-nitrocinnoline is unstable towards hot alkali (Morley, *loc. cit.*), we believe that the complete failure to secure it in the present case was due rather to the nature of the intervening anion (VI). It is striking that the *aci*-derivative (VIII), of similar structure, is rapidly destroyed by alkali (Schofield and Simpson, *J.*, 1945, 512; Keneford, Morley, Simpson, and Wright, *J.*, 1950, 1104). Because of the relative inaccessibility of 4-chloro-5-nitrocinnoline, 5-nitrocinnoline was obtained only in very small amount. The nitration products of cinnoline, m. p. 135—136° and 151—152°, proved to be identical (mixed m. p.) with 8- and 5-nitrocinnoline respectively. Thus, in its orientation the nitration resembles that of quinoline (Schofield, *Quart. Reviews*, 1950, **4**, 382).

3-Methylcinnoline, a pale yellow solid, possessed a characteristic somewhat sickly smell, very similar to that of cinnoline. Like cinnoline it liquefied in air, but more slowly. The other cinnolines described in this paper did not do this, and were odourless. Cinnoline and 3-methylcinnoline were readily soluble in water, whilst 3-chloro-, 3-bromo-, and 5-, 7-, and 8-nitro-cinnoline could be crystallised from this solvent.

Experimental

All extracts and the chloroform used were dried over anhydrous sodium sulphate.

Cinnoline.—4-Hydroxycinnoline (10 g.) and phosphorus oxychloride (30 c.c.) were refluxed together until dissolution occurred (cf. Schofield and Swain, *J.*, 1950, 384), and then warmed ¼ hour at 95°. The product (isolated in the usual way) in chloroform (50 c.c.) was added to toluene-*p*-sulphonylhydrazide (25 g.) (Albert and Royer, *J.*, 1949, 1148) in the same warm solvent (800 c.c.). The red crystals formed were collected after about 1 week (total yield from 30 g. of 4-hydroxycinnoline : 71·5 g., 59%; m. p. 198—200°). The loss probably occurred in the chlorination stage, for small-scale experiments gave quantitative yields based on the 4-chlorocinnoline used. Several crystallisations from acetic acid gave 4-*toluene*-p-*sulphonylhydrazinocinnoline hydrochloride* as crimson needles, m. p. 224—226° (with darkening) (Found : C, 50·6; H, 4·4; N, 15·0. $C_{15}H_{14}O_2N_4S,HCl$ requires C, 51·35; H, 4·3; N, 16·0%).

The above compound (1 g.) was added in portions to sodium carbonate (2 g.; anhyd.) in water (20 c.c.) at 95°. The clear yellow solution formed soon became brown, and deposited some amorphous matter. After being refluxed for ¼ hour the mixture was filtered, and the filtrate was extracted with ether. Removal of the solvent left a brown oil which solidified when chilled. With picric acid in hot alcohol this formed large amber crystals of cinnoline picrate (0·82 g., 80%), m. p. 191—193°, alone and mixed with an authentic specimen.

3-*Methylcinnoline*.—4-Hydroxy-3-methylcinnoline (10 g.; Keneford and Simpson, *J.*, 1948, 354), treated as above, gave 3-*methyl*-4-*toluene*-p-*sulphonylhydrazinocinnoline hydrochloride* (21 g., 92% calc. on 4-hydroxy-3-methylcinnoline) as pink rosettes, m. p. 186—187° (decomp.) (from acetic acid) (Found: C, 52·4; H, 4·5; N, 14·3. $C_{16}H_{16}O_2N_4S,HCl$ requires C, 52·65; H, 4·7; N, 15·35%). Decomposition of this (1 g.) as above gave a red oil (0·42 g.), and thence 3-*methylcinnoline picrate* (86%, crude), khaki prisms, m. p. 175—176·5° (from dioxan) (Found: C, 48·6; H, 2·9. $C_9H_8N_2,C_6H_3O_7N_3$ requires C, 48·3; H, 2·9%).

The product obtained from 14 g. of the toluenesulphonylhydrazine crystallised when cooled. Distillation gave a pale yellow oil (5·08 g., b. p. 106—111°/0·3—0·4 mm.) which crystallised. 3-*Methylcinnoline* separated from ether–light petroleum (b. p. 40—60°) as pale yellow plates, m. p. 58·5—61° (Found: C, 74·9; H, 5·75. $C_9H_8N_2$ requires C, 75·0; H, 5·6%).

3-*Chlorocinnoline*.—3 : 4-Dichlorocinnoline (3·47 g.; Schofield and Swain, *loc. cit.*) and toluene-*p*-sulphonylhydrazide (6·6 g.) were allowed to react in chloroform (200 c.c.). The product (6·83 g., 98%) was deposited in several crops during a fortnight. Slightly impure 3-*chloro*-4-*toluene*-p-*sulphonylhydrazinocinnoline* formed almost colourless crystals, m. p. 167—169° (Found: C, 50·8; H, 4·2. $C_{15}H_{13}O_2N_4SCl$ requires C, 51·6; H, 3·8%), from acetic acid.

The above compound (5·8 g.) was decomposed in the usual way, except that the solution was finally refluxed for 1½ hours. The solution was then filtered from some purple material. Most of the product crystallised on cooling, and more was obtained by extraction with chloroform (total yield: 1·8 g., 75%). 3-*Chlorocinnoline* formed needles, m. p. 90—91° (Found: C, 58·6; H, 3·0. $C_8H_5N_2Cl$ requires C, 58·35; H, 3·1%), from ligroin (b. p. 80—100°).

3-*Bromocinnoline*.—3-Bromo-4-hydroxycinnoline (0·5 g.) and phosphorus oxychloride (3 c.c.) were refluxed for 3 minutes (Schofield and Swain, *loc. cit.*). 3-*Bromo*-4-*chlorocinnoline* (0·54 g., 100%), isolated in the usual way, crystallised from acetone as lemon-yellow blades, m. p. 153—154° (Found: C, 40·1; H, 1·85. $C_8H_4N_2ClBr$ requires C, 39·5; H, 1·6%). This (8 g.) and toluene-*p*-sulphonylhydrazide (15 g.) in chloroform (600 c.c.) gave after a few days 3-bromo-4-toluene-*p*-sulphonylhydrazinocinnoline as a pink solid [14·32 g., m. p. 187—189° (decomp.)] which was not analysed. This (10·6 g.) was decomposed with aqueous sodium carbonate as in the case of the 3-chloro-compound. Some insoluble reddish-brown material was formed and the solution acquired a faint blue fluorescence. After filtration and cooling the product crystallised. It was isolated in the same way as 3-chlorocinnoline. Crystallisation from ligroin (b. p. 80—100°) gave 3-*bromocinnoline* (4·16 g., (80%), m. p. 92—93° (Found: C, 45·7; H, 2·1. $C_8H_5N_2Br$ requires C, 45·95; H, 2·4%). The *picrate* formed yellow prisms, m. p. 118—120° (Found: C, 39·3; H, 1·9. $C_8H_5N_2Br,C_6H_3O_7N_3$ requires C, 38·4; H, 1·8%). 3-Bromo- and 3-chloro-cinnoline showed a mixed m. p. depression of only 2°.

Nitrocinnolines.—2-Amino-nitroacetophenones were obtained by oxidising the 2 : 3-dimethyl-*Bz*-nitroindoles (Schofield and Theobald, *J.*, 1949, 796). Appreciably better yields of the 2-acetamido-nitroacetophenones were gained by modification of the conditions: 2 : 3-dimethyl-7-nitroindole (55 g.) gave 61% of 2-acetamido-3-nitroacetophenone when the stirred reaction mixture (Schofield and Theobald, *loc. cit.*) was kept at 30—35° during the addition of the chromic acid solution, and then stirred for ½ hour at room temperature before being left overnight. On the same scale the appropriate indole provided 57% of 2-acetamido-5-nitroacetophenone. Similarly, in oxidising 6- and 4-nitro-2 : 3-dimethylindole, by keeping the reaction temperatures at 5—12° and 20—25°, the yields of 2-acetamido-4- and 2-acetamido-6-nitroacetophenone were improved to 39% and 46% respectively.

4-Hydroxy-8-nitrocinnoline was best prepared as follows: 2-amino-3-nitroacetophenone (6 g.) in acetic acid (40 c.c.) was stirred and treated with ice-cold sulphuric acid (10 c.c. of concentrated acid and 2 c.c. of water) at <15°. Powdered sodium nitrite (2·7 g.) was then added at 0—5°, and the mixture was kept at 0° overnight and then 2 days at room temperature, before being heated at 95° for ¾ hour. The product (4·37 g.) was precipitated with water, and crystallised from alcohol, giving yellow needles (3·5 g., 55%), m. p. 183—185°.

The 4-chloro-nitrocinnolines were prepared in the usual way. 4-Chloro-8-nitrocinnoline (2·03 g.) in chloroform (90 c.c.) was treated with toluene-*p*-sulphonylhydrazide (4·0 g.) in the same solvent (160 c.c.), and the product (4·2 g.) was collected after 1 week. Initially pink, 8-*nitro*-4-*toluene*-p-*sulphonylhydrazinocinnoline* gave brown needles, m. p. 195—196° (decomp.) (Found: C, 50·2; H, 3·4. $C_{15}H_{13}O_4N_5S$ requires C, 50·1; H, 3·65%), after several crystallisations from acetic acid.

In the same way 4-chloro-6-nitrocinnoline (0·5 g.), toluene-*p*-sulphonylhydrazide (0·9 g.), and chloroform (25 c.c.) gave at first an oil which slowly crystallised and was collected after 1 week (yield, 0·94 g.). One crystallisation provided red prisms of 6-nitro-4-toluene-*p*-sulphonyl-

hydrazinocinnoline, m. p. 190—192° (decomp.) (Found: C, 49·4; H, 3·9%). Morley (*loc. cit.*) gave m. p. 212—213° (decomp.), and the temperature of decomposition may depend on the rate of heating.

Similarly, 4-chloro-7-nitrocinnoline (0·47 g.) gave a product (0·87 g., 98%) which though initially an oil, soon crystallised. Recrystallisation from acetic acid gave at first small red prisms, and finally clusters of orange crystals of *7-nitro-4-toluene-*p*-sulphonylhydrazine*, m. p. 195—196° (decomp.) (Found: C, 50·35; H, 3·55%).

The 5-nitro-compound was obtained as above, but was not analysed.

8-Nitrotoluenesulphonylhydrazinocinnoline (0·57 g.) was added in portions to sodium carbonate (5·7 g.; anhyd.) in water (57 c.c.) at 95°. Heating was continued for ¼ hour and the mixture was then refluxed for ¾ hour, whereupon the intense purple colour was destroyed. The mixture was extracted with ether, and the product was crystallised from water, giving 0·09 g. (36%) of fairly pure material. 8-Nitrocinnoline formed yellow needles, m. p. 132—132·5° (Found: C, 54·5; H, 3·05; N, 23·2. Calc. for $C_8H_5O_2N_3$: C, 54·85; H, 2·9; N, 24·0%). The m. p. was not depressed by admixture with the lower-melting nitration product of cinnoline (Morley, *loc. cit.*).

Obtained in the same way, *7-nitrocinnoline* (51% yield) separated from water as light yellow crystals, m. p. 153—154·5° (Found: C, 54·8; H, 2·85%).

5-Nitrocinnoline prepared by this method formed yellow needles, m. p. 147—148·5°, from water. Morley (*loc. cit.*) recorded m. p. 151—152° for the second nitration product of cinnoline. A somewhat darkened specimen (these compounds deteriorate on keeping), kindly supplied by Dr. Morley, melted at 146—148° after crystallisation from water, and a mixture with the authentic 5-nitro-compound at 147—148°.

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124. *Indoles. Part III.* The Action of* (A) *Ozone, and* (B) *Osmium Tetroxide on Some Indole Derivatives.*

By D. W. Ockenden and K. Schofield.

(*A*) Ozone converted a number of 2 : 3-disubstituted indoles in acetic acid into 2-acylaminoaryl ketones. In ethyl acetate crystalline ozonides were obtained from 3-alkyl-2-aryl-, 2 : 3-dialkyl-, and 2 : 3-diaryl-indoles. Some 1-acylindoles also provided crystalline ozonides.

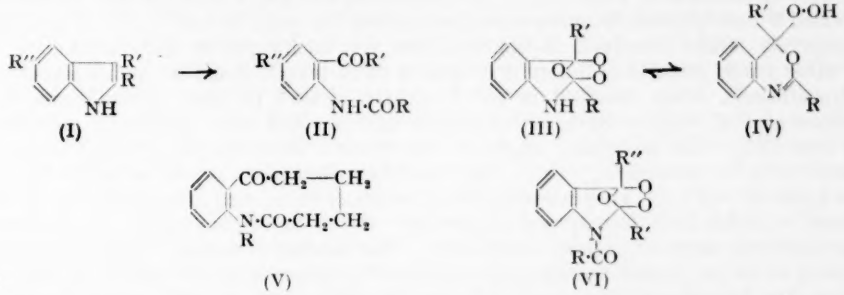
(*B*) Osmium tetroxide in benzene–pyridine converted 1-acetyl- and 1-benzoyl-indoles into crystalline osmic esters, hydrolysable to indole glycols.

(*A*) Oxidative fissions of the indole 2 : 3-double bond (I ⟶ II) have provided routes to various 2-aminoaryl ketones (Schofield and Theobald, *J.*, 1949, 796; 1950, 1505). In extending the synthetic applications of such reactions we considered the use of ozone in certain cases. Various authors have used this reagent in similar reactions, and in some instances the isolation of relatively stable, crystalline ozonides was recorded. Thus (I; R = Ph or *p*-C_6H_4·OMe, R′ = Me, R″ = H, and R = *p*-C_6H_4·OMe, R′ = Me, R″ = OMe) (Mentzer, Molho, and Berguer, *Compt. rend.*, 1949, **229**, 1237; *Bull. Soc. chim.*, 1950, 555), and [I; R = 2-(4 : 5-diethylpyridyl), R′ = Et, R″ = H] (Karrer and Enslin, *Helv. Chim. Acta*, 1949, **32**, 1390) provided crystalline ozonides, hydrolysable to derivatives of type (II). On the other hand, indole, 2-methylindole, skatole, 3-ethylindole, 2 : 3-dimethylindole, and tryptophan (Witkop and Graser, *Annalen*, 1944, **556**, 103), tetrahydrocarbazole (Witkop and Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 2196), and various other indoles (Scholz, *Helv. Chim. Acta*, 1935, **18**, 923; Mentzer, Molho, and Berguer, *loc. cit.*; *Compt. rend.*, 1950, **230**, 760; *Bull. Soc. chim.*, 1950, 782) evidently did not provide isolable ozonides.

Stable, crystalline ozonides of this class are rarely met (Criegee, " Organische Peroxyde,"

* Part II, *J.*, 1950, 1505.

Fortschr. Chem. Forsch., Vol. I, Springer Verlag, Berlin, 1950), and Criegee and Wenner (*Annalen*, 1949, **564**, 9) proved recently that the supposed ozonides from 9 : 10-octalin possessed a different kind of (dimeric) structure. It therefore appeared desirable to determine the molecular weights of representative indole ozonides. Further, since the ozonides described hitherto all arise from 3-alkyl-2-arylindoles, we wished to decide if this type of structure was essential. In view of recent work of Witkop and Patrick (*J. Amer. Chem. Soc.*, 1952, **74**, 3855, 3861) on the interesting reactions of 3-methyl-2-phenylindole ozonide, we record our observations.



Acetic acid, ethyl acetate, formamide, and methanol were used by the authors mentioned above as solvents in which to effect ozonisation of indoles. Our preliminary experiments indicated that formamide was not a sufficiently powerful solvent to serve generally in this field, and we have ozonised each substance examined in both acetic acid and ethyl acetate.

Generally, from experiments in acetic acid, at room temperature, only 2-acylaminoaryl ketones (II) were isolated, as was expected. Thus, 2 : 3-dimethylindole gave 2-acetamidoacetophenone, as described by Witkop and Graser (*loc. cit.*), 2 : 3 : 5- and 2 : 3 : 6-trimethylindole provided 2-acetamido-5- and 2-acetamido-4-methylacetophenone respectively, and 2 : 3-dimethyl-4-nitroindole yielded 2-acetamido-6-nitroacetophenone. The yield (53%) in the last case is considerably better than that (26%) obtained by Schofield and Theobald (*J.*, 1949, 796) by chromic acid oxidation. 3-Methyl-2-phenyl- (cf. Mentzer *et al.*, *loc. cit.*) and 2-methyl-3-phenyl-indole likewise were converted into 2-benzamidoacetophenone and 2-acetamidobenzophenone. Although 2 : 3-diphenyl- and 5-methyl-2 : 3-diphenyl-indole gave 2-benzamido- and 5-methyl-2-benzamido-benzophenone, 6-methyl-2 : 3-diphenylindole gave a mixture.

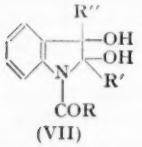
As was expected from the work of Mentzer *et al.* (*loc. cit.*), our results were in some cases different when ethyl acetate at 0° was used as solvent. Although 2 : 3-dimethyl-, 2 : 3-diphenyl-, 2-methyl-3-phenyl-, 2 : 3-dimethyl-4-nitro-, and 2 : 3 : 5-trimethyl-indole, and tetrahydrocarbazole again yielded ketones (II), 3-methyl-2-phenyl- (as found by Mentzer and his associates) and 5- and 6-methyl-2 : 3-diphenyl-indole yielded crystalline ozonides. Further, although 2 : 3 : 6-trimethylindole in ethyl acetate at 0° gave 2-acetamido-4-methylacetophenone, a similar reaction at −20° provided a small yield of a crystalline ozonide. It should be noted that in this work only the theoretical amount of ozone was passed into the solution, and the method used by Witkop and Patrick (*loc. cit.*) for preparing 3-methyl-2-phenylindole ozonide suggests that for this reason our yields of ozonides were not the maximum obtainable. In addition to the previously known type of ozonide from a 3-alkyl-2-arylindole, it is clear that stable derivatives can arise from 2 : 3-dialkyl- and 2 : 3-diarylindoles. Qualitatively, our experience suggests that ozonides from indoles containing an electron-releasing substituent in the *Bz*-ring are possibly the more stable. The experiments on 2 : 3 : 6-trimethylindole indicate that crystalline ozonides might be obtained from a larger range of indoles provided the reaction conditions were carefully chosen.

Molecular-weight determinations in chloroform on the ozonides from 3-methyl-2-phenyl- and 5-methyl-2 : 3-diphenyl-indole, the former confirming the recent determination in acetone by Witkop and Patrick (*loc. cit.*), do not conflict with the formulation of these

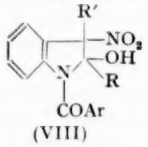
substances in the normal way (III). The American authors adduced evidence that there exists ring-chain tautomerism between (III) and (IV). The ozonides could be crystallised from absolute ethanol or ethyl acetate, but were readily hydrolysed. Thus, 5-methyl-2 : 3-diphenylindole ozonide, when crystallised from non-absolute alcohol, gave 2-benzamido-5-methylbenzophenone. The ozonides decomposed vigorously at the m. p., forming the ketonic products (II) (Witkop and Patrick, *loc. cit.*).

Witkop and Patrick's interpretation of their experiments in terms of tautomerism between (III) and (IV) adds interest to our observations on the action of ozone on 1-acylindoles. In acetic acid, 1-acetyl-2 : 3 : 5-trimethylindole, and 9-acetyltetrahydrocarbazole provided 2-diacetylamino-5-methylacetophenone and the cyclic derivative (V; R = Me·CO) respectively, whilst 1-acetyl-2 : 3-diphenylindole was unchanged by such treatment. On the other hand, 1-acetyl-2 : 3-dimethyl- and -2 : 3 : 5-trimethyl-indole, and 9-acetyltetrahydrocarbazole, when ozonised in ethyl acetate yielded products crystallisable from absolute alcohol, ethyl acetate, or chloroform–ligroin which were apparently ozonides of the type (VI). The molecular weight of the product from 1-acetyltetrahydrocarbazole showed it to be monomeric. Under the conditions used these products were isolated in poor yield (10—15%). They resembled the previously mentioned ozonides in the vigorous manner in which they decomposed on melting. A few experiments with 1-benzoyltetrahydrocarbazole were not entirely satisfactory. The product of ozonisation in ethyl acetate appears to be an impure ozonide, and that from reaction in acetic acid is of uncertain nature (see Experimental section). If correctly represented by (VI), these *N*-acylated ozonides are clearly incapable of ring-chain tautomerism, and that from 9-acetyltetrahydrocarbazole is especially interesting. Witkop and Patrick (*J. Amer. Chem. Soc.*, 1951, **73**, 2196) who obtained (V; R = H) by ozonising tetrahydrocarbazole in methanol at −79° considered that a true ozonide of tetrahydrocarbazole could not exist for steric reasons. This is evidently not so. The low yield of 2 : 3 : 6-trimethylindole ozonide now obtained suggests that these derivatives of alkyl-substituted indoles are highly reactive, and that only when the mobility of the system is restricted as in *N*-acylation can ozonides of the tetrahydrocarbazole group be isolated. Witkop and Patrick (*loc. cit.*) suggested that (VI; R = R″ = Me, R′ = Ph) might be an intermediate in the reaction between 3-methyl-2-phenylindole ozonide and pyridine–acetic anhydride. We hope to examine these substances further.

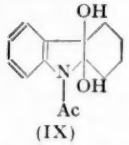
(*B*) Most of the few known glycols of the type (VII) were prepared by Perkin, Plant,



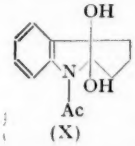
(VII)



(VIII)



(IX)



(X)

and their associates (for a summary see Schofield, *Quart. Reviews*, 1950, **4**, 391) by treating 1-acylindoles with nitric acid in acetic acid. Broadly speaking, 9-acetyl-, 9-cinnamoyl- and 9-carbethoxy-derivatives of 1 : 2 : 3 : 4-tetrahydrocarbazole and 2 : 3-dimethylindole give such glycols, whilst *N*-aroyl derivatives give nitro-alcohols (VIII). 1-Acyl-2 : 3-diphenylindoles merely undergo nuclear nitration, whilst nitro-alcohols are the only addition products to have been isolated from *N*-acyldihydropentindoles. In some cases, though not in the dihydropentindole group, the nitro-alcohols are converted by hot ethanol into the glycol. The compound (X) was prepared by treating *N*-acetyldihydropentindole with chlorine in acetic acid (Plant and Tomlinson, *J.*, 1933, 298). The mode of formation of the glycols, either in nitric–acetic acid, or during halogenation, is unknown. Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614) accounted for striking differences between the behaviour of (IX) and (X) by reference to the size of the third ring. Because of the different methods used in preparing (IX) and (X), and to throw some light on the origin of such glycols, it seemed of value to establish their configuration by alternative syntheses.

Initially we attempted the perhydroxylation of some indoles in acetone by means of dilute aqueous potassium permanganate, a reagent known to convert ethylenes into *cis*-

glycols (Raphael, *J.*, 1949, S 44; Cook and Schoental, *J.*, 1950, 47). 2 : 3-Dimethyl- and -diphenyl-indole, and their *N*-acetyl derivatives, all reduced 1% permanganate solution relatively quickly (by comparison with a blank run) but in each case most of the starting material was recovered unchanged. Presumably a small amount of each indole was very highly oxidised. It is noteworthy that Koelsch (*J. Amer. Chem. Soc.*, 1944, **66**, 1983), using hot concentrated permanganate solution, converted 2 : 3-diphenylindole into a C_{40} compound.

We then turned to the Milas reagent (Milas and Sussman, *J. Amer. Chem. Soc.*, 1936, **58**, 1302), which we used in the way described by Mugdan and Young (*J.*, 1949, 2988). Under these conditions, with 2 : 3-diphenyl- and 2 : 3 : 5-trimethyl-indole, tetrahydrocarbazole, or their *N*-acetyl derivatives, only starting material and small amounts of uncrystallisable products were obtained. Application of the reagent under different conditions might be effective (Witkop and Ek, *J. Amer. Chem. Soc.*, 1951, **73**, 5664).

Finally it was found * that the *N*-acetyl derivatives of tetrahydrocarbazole, dihydropentindole, and 2 : 3-dimethyl-, 2 : 3-diphenyl-, and 2 : 3 : 5-trimethyl-indole with osmium tetroxide in pyridine–benzene gave, quantitatively, highly crystalline, fawn-coloured osmic esters, which were hydrolysed to the glycols (VII; R = Me) in moderate yield. In no case was a crystalline product obtained from the *N*-unsubstituted indoles; in such experiments colloidal osmium was liberated. Indole, skatole, tryptophan, and carbazole behaved similarly, and although pyrrole formed a crystalline complex, nothing could be isolated after hydrolysis (the experiments were on a very small scale). The formation of a glycol from 1-acetyl-2 : 3-diphenylindole is interesting since this substance is not attacked at the 2 : 3-double bond by nitric–acetic acid (Fennell and Plant, *J.*, 1932, 2872), ozone (see above), or bromine (Plant and Tomlinson, *J.*, 1933, 955). Also of interest is the preparation by the same method of glycols from 1-benzoyl-2 : 3-dimethylindole, and 9-benzoyltetrahydrocarbazole. As mentioned above, such glycols are not formed from the 1-benzoylindoles and nitric–acetic acid, nitro-alcohols (VIII) being produced. The compound (IX; Bz instead of Ac) results, however, from the reaction between 9-benzoyltetrahydrocarbazole and chlorine in acetic acid (Plant and Tomlinson, *J.*, 1933, 298), and from the corresponding nitro-alcohol in hot ethanol (Plant and Rutherford, *J.*, 1929, 1970).

Criegee's work (*Annalen*, 1936, **522**, 75; 1942, **550**, 99) strongly suggests that the products now described are *cis*-glycols, although the failure of (IX) to provide an acetonyl derivative (Witkop, *J. Amer. Chem. Soc.*, 1950, **72**, 613) is puzzling. If in nitric–acetic acid media the *cis*-glycols arise from ionic processes it is not likely that they are primary products. If their precursors are nitro-alcohols (cf. VIII) the latter would presumably be *trans*-forms. However, Witkop and Ek (*J. Amer. Chem. Soc., loc. cit.*) state that the presence of the nitrogen alone in a related glycol makes the *trans*-form susceptible to easy inversion. There seems to be little evidence on this point, and the nitro-alcohols require investigation.

Some of the indoles used in this work were prepared by the Fischer synthesis with the boron trifluoride-ether complex as the catalyst, in acetic acid solution (Snyder and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 2454). In this way 2 : 3-dimethyl-, 2-methyl-3-phenyl-, 5-methyl-2 : 3-diphenyl-, and 2 : 3 : 5-trimethyl-indole were obtained in good yield. 2-Methyl-3-phenylindole was previously prepared by Trenkler (*Annalen*, 1888, **248**, 11) who used zinc chloride or alcoholic hydrochloric acid as the catalyst in the cyclisation of phenylacetone phenylhydrazone, and the structure of the compound is now proved by its conversion into 2-acetamidobenzophenone.

Experimental

2 : 3 : 5-*Trimethylindole*.—Ethyl methyl ketone *p*-tolylhydrazone (12·2 g.; obtained by heating equivalent quantities of the ketone and *p*-tolylhydrazine at 95° for 1 hour and then drying the product in ether), boron trifluoride–ether (8·6 g.), and acetic acid (120 c.c.) were refluxed for 3 hours. The hot mixture was filtered and concentrated, giving the indole (6·2 g.; m. p. 120—121°). Further concentration of the mother-liquor and crystallisation of the residue from alcohol brought the yield to 8·75 g. (80%).

* A preliminary account of this work was given in *Nature*, 1951, **168**, 603.

Alternatively, the hydrazone [from the ketone (6·35 g.) as above] was treated gradually with powdered anhydrous zinc chloride (13·9 g.), and the mixture was heated gently until a vigorous reaction set in. When this had subsided the product was isolated by steam-distillation and extraction of the distillate with ether. Concentration gave the substantially pure indole (10·2 g., 72%). 2 : 3 : 5-Trimethylindole formed fawn plates, m. p. 121—122° (Found: C, 82·4; H, 8·2. Calc. for $C_{11}H_{13}N$: C, 82·9; H, 8·2%). This compound has been obtained previously (Beilstein's "Handbuch der organischen Chemie," 4th edn., Vol. XX; Hickinbottom, *J.*, 1934, 1981; Jenetzky and Verkade, *Rec. Trav. chim.*, 1945, **65**, 691) but not by the Fischer synthesis.

The indole (3 g.), acetic anhydride (20 c.c.), and one drop of 2N-sulphuric acid were refluxed for 12 hours. The solution was poured into iced water, and the product (2·6 g.) was collected. *1-Acetyl-2 : 3 : 5-trimethylindole* separated from aqueous methanol as cream prisms, m. p. 85—86° (Found: C, 77·7; H, 7·5. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5%).

2-Methyl-3-phenylindole.—Benzyl methyl ketone phenylhydrazone (1 g.), acetic acid (10 c.c.), and boron trifluoride–ether (0·73 g.) were refluxed for 3 hours. The crude product obtained by filtration and concentration crystallised from light petroleum (b. p. 40—60°) as cream prisms (0·6 g., 65%), m. p. 58—60°. Trenkler (*loc. cit.*) gives m. p. 59—60°. The material from a similar experiment with 6 g. of the hydrazone was passed in benzene over alumina, giving 2-methyl-3-phenylindole in the same yield as above. The column showed a second yellow band, but elution gave only very small amounts of intractable oils. If 2-benzylindole is formed in the experiment it could only be as a trace.

5-Methyl-2 : 3-diphenylindole.—Deoxybenzoin and *p*-tolylhydrazine were heated in equivalent amounts for 1 hour at 95°; the product crystallised from alcohol as discoloured needles (71%), m. p. 118—120°, which quickly deteriorated. This hydrazone (5 g.), boron trifluoride–ether (2·36 g.), and acetic acid (50 c.c.) were refluxed for 3 hours. The hot solution was filtered and concentrated. Addition of water and crystallisation of the product from aqueous alcohol gave white needles (3·85 g., 82%), m. p. 148—150°. The indole (3·4 g., 73%) was also obtained by heating the hydrazone (5 g.) with concentrated hydrochloric acid (50 c.c.) for 4 hours at 95°, and crystallising the product from aqueous alcohol. 5-Methyl-2 : 3-diphenylindole exhibited deep blue fluorescence in aqueous alcohol, and when pure formed needles, m. p. 150—151° (Found: C, 90·2; H, 6·5. Calc. for $C_{21}H_{17}N$: C, 89·0; H, 6·1%). Ritchie (*Proc. Roy. Soc. N.S. Wales*, 1946, **80**, 33) gives m. p. 153°.

9-Acetyl-1 : 2 : 3 : 4-tetrahydrocarbazole.—The following method was preferable to that using anhydrous potassium acetate, and appears simpler than that due to Witkop (*J. Amer. Chem. Soc.*, 1950, **72**, 614). Tetrahydrocarbazole (5 g.), acetic anhydride (25 c.c.), and a trace of camphorsulphonic acid were refluxed for 7 hours. The solvent was removed under reduced pressure, and distillation gave the product (b. p. 230—232°/20 mm.), which was crystallised from alcohol, yielding 3·1 g. (50%), m. p. 72—74°.

Experiments with Ozone.—The results (Table 1) were obtained by treating the indole (0·5 g.) with approx. 5% ozonised oxygen until the theoretical amount (as indicated by titration) of ozone had been absorbed. Experiments in acetic acid were carried out at room temperature, those in ethyl acetate at 0°. In the first case the product was isolated by basification and ether-extraction, and in the second by concentration at room temperature. The m. p.s of the ozonides, being decomposition temperatures, depended considerably on the rate of heating.

Products. (2) *2-Acetamido-5-methylacetophenone* gave fawn plates (Found: C, 69·4; H, 6·7. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·9%). This compound (0·5 g.) was heated at 95° for 2 hours with concentrated hydrochloric acid (5 c.c.), water (5 c.c.), and alcohol (10 c.c.). After cooling, the solution was basified and chilled, and the resulting 2-amino-5-methylacetophenone was crystallised from ether–light petroleum (b. p. 40—60°), forming yellow plates, m. p. 41—42° (Found: C, 72·5; H, 7·7%). Giacalene and Russo (*Gazzetta*, 1935, **65**, 1127) gave m. p. 50—51°.

(3) *2 : 3 : 6-Trimethylindole ozonide* formed colourless crystals (Found: C, 64·1; H, 5·9. $C_{11}H_{13}O_3N$ requires C, 63·8; H, 6·3%). The m. p. of 2-acetamido-4-methylacetophenone (Found: C, 69·85; H, 7·0. Calc. for $C_{11}H_{13}O_2N$: C, 69·1; H, 6·85%) was not depressed by admixture with authentic material (Keneford, Morley, and Simpson, *J.*, 1948, 1702).

(5) (V; R = H). This compound has usually been described as being faintly yellow. Our specimen, m. p. 154—156°, was colourless (Found: C, 70·9; H, 6·5. Calc. for $C_{12}H_{13}O_2N$: C, 70·9; H, 6·4%).

(6) 2-Acetamidobenzophenone formed prisms (Found: C, 74·6; H, 5·4. Calc. for $C_{15}H_{13}O_2N$: C, 75·3; H, 5·5%), and did not depress the m. p. of a genuine specimen.

(7) The ozonide [Found: C, 71·5; H, 4·8; N, 4·8%; *M* (in acetone), 246. Calc. for

$C_{15}H_{13}O_3N$: C, 70·6; H, 5·1; N, 5·5%; *M*, 255] was recovered unchanged by evaporation of the solution used in determining the molecular weight. 2-Benzamidoacetophenone (Found: C, 75·3; H, 5·1. Calc. for $C_{15}H_{13}O_2N$ C, 75·3; H, 5·5%).

(9) 5-*Methyl*-2 : 3-*diphenylindole ozonide* formed prisms [Found: C, 75·6; H, 5·2; N, 3·7%; *M* (in acetone), 330. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·2; N, 4·2%; *M*, 332] and was recovered unchanged from the mol.-wt. determination. 2-Benzamido-5-methylbenzophenone gave cream prisms, m. p. 115—117° (Found: C, 79·4; H, 5·4. Calc. for $C_{21}H_{17}O_2N$: C, 80·0; H, 5·4%). Chattaway and Lewis (*J.*, 1904, **85**, 589) gave m. p. 118°.

(10) 6-*Methyl*-2 : 3-*diphenylindole ozonide* formed prisms (Found: C, 76·1; H, 5·3%).

(11) 1-*Acetyl*-2 : 3-*dimethylindole ozonide* gave very small crystals (Found: C, 62·1; H, 5·8; N, 5·5. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·6; N, 6·0%).

(12) 1-*Acetyl*-2 : 3 : 5-*trimethylindole ozonide* formed small crystals (Found: C, 63·3; H, 6·1. $C_{13}H_{15}O_4N$ requires C, 62·6; H, 6·1%), and 2-*diacetylamino*-5-*methylacetophenone* plates (Found: C, 66·4; H, 6·2. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·5%).

(13) Impure 9-acetyltetrahydrocarbazole ozonide gave small crystals [Found: C, 62·8; H, 5·6%; *M* (in chloroform), 240. $C_{14}H_{15}O_4N$ requires C, 64·3; H, 5·8%; *M*, 261], and (V; R = Ac) small prisms (Found: C, 68·7; H, 6·5. $C_{14}H_{15}O_3N$ requires C, 68·55; H, 6·2%).

9-Benzoyltetrahydrocarbazole (0·5 g.) was ozonised in ethyl acetate (25 c.c.), and the oily product obtained by removing the solvent was triturated with alcohol. The *ozonide* (40 mg.) had m. p. 220—225° (decomp.) (from chloroform–ligroin) (Found: C, 68·6; H, 5·2. $C_{19}H_{17}O_4N$ requires C, 70·5; H, 5·3%). A similar experiment in acetic acid (30 c.c.), by working up in the usual way, yielded 0·3 g. of crude product, which after several crystallisations from methanol

TABLE 1.

Indole	EtOAc (c.c.)	AcOH + H_2O (c.c.)		Product [a]	Solvent [b]	Final M. p.	Yield, %
(1) 2 : 3-Dimethyl	20	—	—	2-Acetamidoacetophenone	1	67—70° [c]	52
	—	15	5	"	"	"	49
(2) 2 : 3 : 5-Trimethyl	25	—	—	2-Acetamido-5-methylacetophenone	2	123—125	50
	—	25	5	"	"	"	47
(3) 2 : 3 : 6-Trimethyl [d]	25	—	—	Ozonide	3	138	8
	—	25	—	2-Acetamido-4-methylacetophenone	4	75—77	45
(4) 2 : 3-Dimethyl-4-nitro	25	—	—	2-Acetamido-6-nitroacetophenone	5	143—144	53
	—	40	—	"	"	"	"
(5) Tetrahydrocarbazole	25	—	—	(V; R = H)	6	152—154	40
	—	25	5	"	"	154—156	44
(6) 2-Methyl-3-phenyl	25	—	—	Tar [e]	—	—	—
	—	30	5	2-Acetamidobenzophenone	7	71—73	40
(7) 3-Methyl-2-phenyl	25	—	—	Ozonide	3	157—158 [f]	66
	—	25	5	2-Benzamidoacetophenone	7	97—99	48
(8) 2 : 3-Diphenyl	20	—	—	2-Benzamidobenzophenone	5	85—87	55
	—	15	5	"	"	"	57
(9) 5-Methyl-2 : 3-diphenyl	25	—	—	Ozonide	3	158—160	50
	—	50	5	2-Benzamido-5-methylbenzophenone	8	115—117	45
(10) 6-Methyl-2 : 3-diphenyl	25	—	—	Ozonide	6	159—160	52
	—	35	—	Mixture	—	—	—
(11) 1-Acetyl-2 : 3-dimethyl	25	—	—	Ozonide	3	227—228	10
	—	35	—	Small yield of crude ozonide	—	—	—
(12) 1-Acetyl-2 : 3 : 5-trimethyl	25	—	—	Ozonide	6	200—215	25
	—	25	—	2-Diacetylamino-5-methylacetophenone	7	119—121	26
(13) 9-Acetyltetrahydrocarbazole	25	—	—	Ozonide	9	232	10
	—	25	5	(V; R = Ac)	8	127—129	35

[a] See main text for comments. [b] 1, Aq. $COMe_2$. 2, MeOH. 3, Abs. EtOH. 4, C_6H_6–ligroin. 5, Aq. EtOH. 6, EtOAc. 7, Et_2O–ligroin. 8, EtOH. 9, $CHCl_3$–ligroin. [c] Alone and mixed with an authentic specimen. [d] Ockenden and Schofield, unpublished. [e] Even at −20°. [f] Mentzer, Molho, and Berguer, *loc. cit.*

TABLE 2.

Substance	Wt. (g.)	Yield of osmic ester (g.)	Wt. (g.) of crude product	Solvent	M. p. of pure product
(1) 9-Acetyltetrahydrocarbazole	0·084	0·260	0·017	C_6H_6	203—204°
(2) 8-Acetyldihydropentindole	0·079	0·214	0·060	,,	149—151
(3) 1-Acetyl-2 : 3-dimethylindole ...	0·074	0·222	0·060	,,	130—133
(4) 1-Acetyl-2 : 3 : 5-trimethylindole	0·081	0·200	0·061	,,	102—108
(5) 1-Acetyl-2 : 3-diphenylindole	0·123	0·223	0·032	,,	206—208
(6) Pyrrole	0·027	0·130	0·010	—	—
(7) 1-Benzoyl-2 : 3-dimethylindole ...	0·200	0·410	0·100	C_6H_6–ligroin	215—218
(8) 9-Benzoyltetrahydrocarbazole ...	0·216	0·430	0·100	,,	144—147

(1) Leaflets (Found: C, 68·3; H, 7·1. Calc. for $C_{14}H_{17}O_3N$: C, 68·1; H, 6·9%), identical with authentic material (Perkin and Plant, *J.*, 1923, **123**, 676). (2) Prisms (Found: C, 66·9; H, 4·6. Calc. for $C_{12}H_{15}O_3N$: C, 66·9; H, 6·5%), identical with a genuine specimen (Plant and Tomlinson, *J.*, 1933, 298). (3) Prisms (Found: C, 65·9; H, 7·2. Calc. for $C_{12}H_{13}O_3N$: C, 65·1; H, 6·8%). Plant and Whitaker (*J.*, 1940, 283) give m. p. 132—134°. (4) Needles (Found: C, 66·3; H, 7·4. $C_{13}H_{17}O_3N$ requires C, 66·3; H, 7·3%). The m. p. could not be improved. (5) Prisms (Found: C, 76·8; H, 5·6. $C_{22}H_{19}O_3N$ requires C, 76·5; H, 5·5%). (7) Prisms (Found: C, 74·3; H, 6·9. $C_{17}H_{17}O_3N,\frac{1}{2}C_6H_6$ requires C, 74·5; H, 6·3%). (8) Prisms (Found: C, 74·1; H, 6·4. Calc. for $C_{19}H_{19}O_3N$: C, 73·7; H, 6·2%). Plant and Tomlinson (*loc. cit.*) give m. p. 144—146°.

provided needles, m. p. 180—182°, of a *hydrate* (Found: C, 66·1; H, 6·2. $C_{19}H_{17}O_3N,2H_2O$ requires C, 66·4; H, 6·2%).

Experiments with Osmium Tetroxide.—Except in experiments (7) and (8) which were on twice the scale, the indole, osmium tetroxide (0·100 g.), benzene (3·3 c.c.), and pyridine (0·065 c.c.) were left together overnight. The fawn crystals were collected, dried in air, and refluxed with alcohol (5 c.c.), water (5 c.c.), and sodium sulphite (1 g.) for 1 hour. The hot mixture was filtered, the black residue was washed with hot alcohol, and the combined filtrate and washings were concentrated and extracted with chloroform. The extract was dried (Na_2SO_4), the chloroform was removed, and the product was recrystallised (Table 2).

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125. ω-2′-*Furylalkane Derivatives.*

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The use of palladised strontium carbonate as a catalyst permits the hydrogenation of the alkene side chain in 2′-furylalkenes without reduction of the nucleus. Application of this reaction to the preparation of some ω-2′-furyl derivatives is described.

THE synthesis of ω-2′-furylalkane derivatives from furfuraldehyde through alkenes of the type $C_4H_3O{\cdot}[CH{:}CH]_n{\cdot}CH_2X$ is hindered by the instability of the furan nucleus (cf. Jones and Taylor, *Quart. Reviews*, 1950, **4**, 196). It has now been found that hydrogenation in the presence of palladised strontium carbonate proceeds without attack on the nucleus, except in such compounds as ethyl β-2′-furylacrylate which contain a cationoid system. The potassium salt of the corresponding acid is, however, reducible in aqueous solution with the same catalyst to the desired ω-2′-furylalkane acid uncontaminated with tetrahydrofuryl derivatives.

Besides its ease of reduction the furan nucleus has great sensitivity to acids, thionyl chloride, and phosphorus, aluminium, and stannic halides. For this reason the Friedel–Crafts reaction has not been used with success; not many of the ω-furylalkyl halides have been prepared and the iodides appear to be unknown. By the action of sodium iodide on the toluene-*p*-sulphonates of the alcohols it has been possible to convert ω-2′-furylalkanols into the alkyl iodides in overall yields of 70%. A series of ω-2′-furylalkanecarboxylic acids has been prepared and converted into the amides. Previously only the anilides were known.

All the furyl derivatives prepared are unstable to acids. The apparent stability to

aqueous acids conferred by a long methylene chain is due to sparing solubility in the reagent: it disappears when aqueous-alcoholic acids are used.

Where the refraction was measured the observed values showed the "negative exaltation" characteristic of the furan nucleus. The melting points of the ω-furylalkanecarboxylic acids, $C_4H_3O\cdot[CH_2]_n\cdot CO_2H$, from furylpropionic to furylheptanoic, display a "reverse alternation," the acids with an odd total number of carbon atoms in the side chain being higher-melting than their next homologues: when $n = 2$, 3, 4, 5, or 6, the melting points are 58°, (oil), 43°, 19°, 36°, respectively.

Experimental

Intermediates, Acids, etc.—β-*2-Furylacraldehyde* (cf. Röhmer, *Ber.*, 1898, **31**, 283). To sodium hydroxide (10 g.) in water (2 l.) furfuraldehyde (34 c.c.) was added, followed by acetaldehyde (100 c.c.), with vigorous swirling. The mixture was heated on a water-bath to 40°, then after 5 minutes cooled to 25° and extracted with chloroform. The aldehyde (35 g.; 70%, based on furfuraldehyde) boiled at 110—115°/15 mm. and solidified. Redistillation at 0·1 mm. and crystallisation from benzene–light petroleum gave needles, m. p. 53° (König, *Ber.*, 1925, **58**, 2559, gives m. p. 54°) (Found: C, 68·9; H, 5·3. Calc. for $C_7H_6O_2$: C, 68·8; H, 5·0%). The semicarbazone, plates from alcohol, melted at 212—213° (Found: N, 23·2. Calc. for $C_8H_9O_2N_3$: N, 23·5%); Röhmer gave m. p. 215—219°.

Burdick and Adkins's procedure (*J. Amer. Chem. Soc.*, 1934, **56**, 441) gave only 45% yields but was preferred for large-scale preparations.

5-2′-Furylpenta-2 : 4-dienal. This was prepared by the method of Hinz, Meyer, and Schücking (*Ber.*, 1943, **76**, 676) by adding acetaldehyde slowly to a *cold*, well-stirred alkaline suspension of furfuraldehyde. The fraction of the product boiling at 130—160°/15 mm. crystallised from light petroleum in pale yellow needles, m. p. 65—66° (yield, 20%). Hinz, Meyer, and Schücking record m. p. 66°.

7-2′-Furylhepta-2 : 4 : 6-trienal could not be isolated from the mixture obtained by condensing 3-2′-furylacraldehyde and crotonaldehyde in presence of piperidine acetate (cf. Schmidt, *Annalen*, 1941, **547**, 270), but the reaction yields 11-2′-furylundeca-2 : 4 : 6 : 8 : 10-pentaenal. Extraction of the crude product (20 g., from 20 g. of furylacraldehyde and 25 g. of crotonaldehyde) with boiling toluene gave 6—7 g. of the deep red undecapentaenal, m. p. 107—110°, the remainder being tar.

β-2-Furylacrylic acid (*Org. Synth.*, 1945, **25**, 51) melted at 141°.

5-2′-Furylpent-2-enoic acid, made from β-2-furylpropaldehyde, malonic acid, pyridine, and a trace of piperidine (yield 79%), had b. p. 160—170°/0·3 mm., and formed needles, m. p. 75—76°, from light petroleum (b. p. 40—60°) (Found: C, 65·2; H, 6·1. $C_9H_{10}O_3$ requires C, 65·1; H, 6·1%).

5-2′-Furylpenta-2 : 4-dienoic acid. By Röhmer's method (*loc. cit.*) β-2-furylacrylic acid (11 g.), sodium acetate, and acetic anhydride at 175—180° gave only 0·1 g. of acid, m. p. 153°. By Hinz, Meyer, and Schücking's method (*loc. cit.*) furylacraldehyde, ethyl acetate, and sodium ethoxide gave an ester (62%), b. p. 145—150°/10 mm., m. p. 22—23° (Found: C, 68·9; H, 7·0. Calc. for $C_{11}H_{12}O_3$: C, 68·8; H, 6·3%). Hinz, Meyer, and Schücking give m. p. 14—15°. This ester was rapidly hydrolysed by aqueous-alcoholic potassium hydroxide to the acid, m. p. 153—154° (85% yield).

7-2′-Furylhepta-2 : 4 : 6-trienoic acid. 5-2′-Furylpenta-2 : 4-dienal (54 g., 0·3 mole) in anhydrous ethyl acetate (100 c.c.) was added dropwise during 2 hours to a vigorously stirred suspension of powdered sodium (10·0 g., 0·43 g.-atom) in ethyl acetate (150 c.c.) containing ethanol (1 c.c.) at −10° to −15°, and the mixture stirred for 3 hours. The resulting *ester* boiled at 135—140°/0·1 mm. and crystallised from 90% alcohol as yellow needles, m. p. 81—82° (47 g., 59%) (Found: C, 71·9; H, 6·7. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·4%). The derived acid melted at 194—196°. Hausser, Kuhn, Smakula, and Deutsch (*Z. physikal. Chem.*, 1935, *B*, **29**, 378) give m. p. 195—200° (corr.). The *amide*, pale yellow needles from 90% alcohol, melted at 210—211° (Found: N, 7·1. $C_{11}H_{11}O_2N$ requires N, 7·4%).

ω-*2′-Furylalkanols.*—*3-2′-Furylpropanol.* β-2-Furylacraldehyde by the Meerwein–Ponndorf method gave, in 6 hours, 3-2′-furylprop-2-enol (90%), b. p. 74—76°/0·2 mm., n_D^{20} 1·5445 (Found: C, 67·6; H, 6·7. Calc. for $C_7H_8O_2$: C, 67·8; H, 6·5%). The colourless liquid gave a 1-naphthylurethane, m. p. 93—94°. Bray and Adams (*J. Amer. Chem. Soc.*, 1927, **49**, 2101) give n_D^{27} 1·5520 and 1-naphthylurethane, m. p. 93—93·5°.

Reduction of the propenol (27 g.) in ethanol (80 c.c.) with hydrogen at 4 atm. in presence of

palladised strontium carbonate (2 g., from 1 g. of palladium chloride on 35 g. of commercial strontium carbonate) was complete in 10 minutes, giving the propanol (22 g.), b. p. 122°/15 mm., n_D^{20} 1·4795, d_4^{20} 1·060, $[R_L]_D^{20}$ 33·8 (Calc.: 34·56) (Found: C, 66·7; H, 8·0. Calc. for $C_7H_{10}O_2$: C, 66·8; H, 7·9%). Bray and Adams (*loc. cit.*) give b. p. 201—208°/747 mm., n_D^{25} 1·4760, d_{20}^{20} 1·0613 (1-naphthylurethane, m. p. 49°).

For 4-2′-furylbutanol, see Hofmann, Bridgwater, and Axelrod, *J. Amer. Chem. Soc.*, 1949, **71**, 1253.

5-2′-Furylpentanol. (*a*) 5-2′-Furylpenta-2 : 4-dienal (26·5 g.) in *iso*propanol (500 c.c.) with distilled aluminium *iso*propoxide (6·3 g.) gave, in 3·5 hours, the unsaturated alcohol (21·1 g., 80%) free from aldehyde. This (a pale yellow solid), crystallised from benzene–light petroleum, had m. p. 50—51°. The colourless crystals rapidly formed a dark gum, and a satisfactory analysis could not be obtained. The freshly distilled 5-2′-furylpenta-2 : 4-dienol was reduced in 6 minutes with hydrogen at 4 atm. (Pd–$SrCO_3$). *5-2′-Furylpentanol* (yield 93%) had b. p. 125—127°/15 mm., n_D^{20} 1·4798, d_4^{20} 1·023, $[R_L]_D^{20}$ 42·8 (Calc. 43·8) (Found: C, 70·2; H, 9·3. $C_9H_{14}O_2$ requires C, 70·1; H, 9·2%). The 1-naphthylurethane, colourless needles from light petroleum (b. p. 40—60°), melted at 58—59°. Hofmann (*J. Amer. Chem. Soc.*, 1945, **67**, 421) gives m. p. 58—58·5° (he did not purify the pentanol). (*b*) 5-2′-Furylpenta-2 : 4-dienal (23·5 g.) in ethanol (70 c.c.) was reduced with hydrogen at 160°/164 atm. and copper chromite (Connors, Folkers, and Adkins, *J. Amer. Chem. Soc.*, 1932, **54**, 1139). Reduction was complete in 10 minutes. The product, which was free from aldehydes (Schiff and Angeli–Rimini tests), had n_D^{20} 1·4798 (Found: C, 70·1; H, 9·1%). (*c*) Reduction of 5-2′-furylpenta-2 : 4-dienal with hydrogen at 4 atm. and Raney nickel gave, in 11 minutes at room temperature, a product showing positive tests for the aldehyde group and *also* a high percentage of hydrogen (Found: C, 68·9; H, 11·3. *5-2′-Tetrahydrofurylpentanol*, $C_9H_{18}O_2$, requires C, 68·3; H, 11·5%). It was inferred that nuclear reduction had occurred.

7-2′-Furylheptanol. (*a*) Attempts to produce this alcohol by reduction of the crude mixture of polyene aldehydes from the condensation of furylacraldehyde and crotonaldehyde led only to a small yield of an impure product. (*b*) Reduction of 7-2′-furylheptanoic acid (see below) in ether with lithium aluminium hydride gave in 45 minutes an *alcohol*, b. p. 92—94°/0·2 mm., n_D^{20} 1·4797, d_4^{20} 0·987, $[R_L]_D^{20}$ 52·45 (Calc.: 53·05) (Found: C, 72·2; H, 9·8. $C_{11}H_{18}O_2$ requires C, 72·5; H, 10·0%). The 1-*naphthylurethane*, needles from light petroleum (b. p. 40—60°), melted at 70—71° (Found: N, 4·0. $C_{22}H_{25}O_3N$ requires N, 4·0%).

11-2′-Furylundecanol. 11-2′-Furylundeca-2 : 4 : 6 : 8 : 10-pentaenal (the crude mixture of unsaturated aldehydes described above; 22·0 g.) was finely powdered and reduced in 3 batches with ethanol (80 c.c.), palladised strontium carbonate (2·0 g.), and hydrogen at 5 atm. for each batch. The colourless distillates of b. p. 105—125°/0·1 mm. (9·1 g.) were combined and immediately reduced (Meerwein–Ponndorf) giving 7·0 g. of the alcohol. Distillation gave the *alcohol*, b. p. 132—135°/0·03 mm., n_D^{20} 1·4795, d_4^{20} 0·949, $[R_L]_D^{20}$ 71·3 (Calc.: 71·50) (Found: C, 75·6; H, 11·1. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). The 1-*naphthylurethane*, needles from light petroleum (b. p. 40—60°), melted at 73—74° (Found: N, 3·3. $C_{26}H_{33}O_3N$ requires N, 3·4%).

ω-2′-Furylalkyl Halides.—*1-Bromo-3-2′-furylpropane.* To a solution of 3-2′-furylpropanol (10·5 g., 0·085 mole) in boiling dry ether (100 c.c.), phosphorus tribromide (4·0 g., 0·015 mole) in ether (50 c.c.) was added dropwise during 30 minutes. The dark solution was then refluxed for 3 hours and left overnight at room temperature; a dark mass of acid phosphorous esters separated. From the ethereal layer the *bromide* (4·0 g., 27%) was obtained, having b. p. 88—91°/15 mm., n_D^{20} 1·5011 (Found: Br, 42·1. C_7H_9OBr requires Br, 42·3%).

1-Bromo-5-2′-furylpentane was similarly prepared from the pentanol (10·0 g., 0·064 mole) and phosphorus tribromide (8·6 g., 0·032 mole) but the mixture was refluxed for 8·5 hours. The product (41% yield) had b. p. 124—127°/15 mm., n_D^{20} 1·4996 (Found: Br, 36·7. $C_9H_{13}OBr$ requires Br, 36·8%).

1-2′-Furyl-3-iodopropane. To 3-2′-furylpropanol (20·5 g., 0·17 mole) in dry pyridine (120 c.c.) at −15°, toluene-*p*-sulphonyl chloride (38·1 g., 0·2 mole) was added in 3 portions (temp. held below 0°) and the mixture kept for 3 hours in an ice–salt bath (cf. Tipson, *J. Org. Chem.*, 1944, **9**, 235). Water (10 × 2 c.c.) was added and the mixture then slowly poured into ice-water (600 c.c.) containing concentrated hydrochloric acid (200 c.c.). The pink oil which separated was extracted with the aid of sodium chloride and ether (4 × 200 c.c.); it (45·4 g., 79%) did not crystallise.

To a solution of dried sodium iodide (35 g., 0·2 mole) in dry acetone (250 c.c.) the toluene-*p*-sulphonate (45 g., 0·18 mole) was added and the mixture left at room temperature for 48 hours. After a few minutes sodium toluene-*p*-sulphonate began to separate. This salt was collected

and dried at 140° (24·5 g., 98%). After the acetone had been removed (12″ Dufton column), water (200 c.c. saturated with sodium chloride) was added and the mixture extracted with ether. The extracts, washed with 1% thiosulphate solution and then dried ($MgSO_4$), yielded the *iodide* (27·7 g., 91%), b. p. 94—96°/15 mm., n_D^{20} 1·55, d_4^{20} 1·577 (Found: I, 54·1. C_7H_9OI requires I, 53·8%). The overall yield from the alcohol was 72%.

1-2′-*Furyl*-5-*iodopentane*. Similar methods gave the crude pentyl toluene-*p*-sulphonate (87%) and thence the *iodide* (92%), b. p. 124—126°/16 mm., n_D^{20} 1·5331, d_4^{20} 1·489, $[R_L]_D^{20}$ 54·7 (Calc.: 55·07) (Found: I, 47·4. $C_9H_{13}OI$ requires I, 48·1%).

1-2′-*Furyl*-11-*iodoundecane*. This iodide (60% yield from the undecanol) could not be distilled or crystallised.

ω-2′-*Furylalkyl Cyanides*.—1-Bromo-3-2′-furylpropane with aqueous-alcoholic potassium cyanide gave 3-2′-*furylpropyl cyanide*, b. p. 104—108°/10 mm., n_D^{20} 1·4712 (70% yield) (Found: N, 10·3. C_8H_9ON requires N, 10·4%).

5-2′-*Furylpentyl cyanide*, similarly prepared in 87% yield, had b. p. 147—149°/20 mm., n_D^{20} 1·4731 (Found: N, 8·5. $C_{10}H_{13}ON$ requires N, 8·6%). The cyanide from crude 1-2′-furyl-11-iodoundecane was not purified.

ω-2′-*Furyl-carboxylic Acids and Their Amides*.—β-2-*Furylpropionic acid*. A solution of β-2-furylacrylic acid (13·8 g., 0·1 mole) in water (60 c.c.) containing potassium hydroxide (8·0 g.) and palladised strontium carbonate (2·0 g.) was reduced in 3 hours at room temperature with hydrogen at 4—5 atm. The solution was poured on crushed ice (10·0 g.) and vigorously stirred while hydrochloric acid was added until the mixture was acid to Congo-red. The precipitated solid was *quickly* filtered off; after being dried it was distilled, and then crystallised from light petroleum (b. p. 40—60°); it melted at 57—58°. The yield was 91% (Found: C, 59·8; H, 5·5. Calc. for $C_7H_8O_3$: C, 60·0; H, 5·7%). Amstutz and Plucker (*J. Amer. Chem. Soc.*, 1941, **63**, 206) give m. p. 56·5—57·6°. To the acid (1 g.) in ether (5 c.c.) distilled phosphorus trichloride (0·4 g.) in ether (1 c.c.) was added and the mixture left for 1 hour at room temperature. The ether was removed and the liquid poured immediately with vigorous stirring into aqueous ammonia (20 c.c.; *d* 0·880) and crushed ice (10 g.). The *amide* (75%), crystallised from water containing a little ethanol, melted at 107—108° (Found: N, 9·5. $C_7H_9O_2N$ requires N, 10·0%).

γ-2-*Furylbutyric acid*. Hydrolysis of 3-2′-furylpropyl cyanide with aqueous-alcoholic potassium hydroxide for 8 hours gave the oily acid (80%), b. p. 108—110°/0·4 mm., n_D^{20} 1·4796, d_4^{20} 1·1307, $[R_L]_D^{20}$ 38·7 (calc.: 39·19) (Hofmann, Bridgwater, and Axelrod, *J. Amer. Chem. Soc.*, 1949, **71**, 1253, give b. p. 94—117°/0·03 mm.) (Found: C, 62·3; H, 6·8. Calc. for $C_8H_{10}O_3$: C, 62·3; H, 6·5%). The *amide*, made as above, crystallised from water with a little ethanol in plates, m. p. 88—89° (Found: N, 9·4. $C_8H_{11}O_2N$ requires N, 9·2%).

δ-2-*Furylvaleric acid*. (*a*) Hydrogenation of potassium 5-2′-furylpenta-2 : 4-dienoate in water (with Pd–$SrCO_3$) at 4—5 atm. was complete in 40 minutes at room temperature and gave a solid acid (88%), m. p. 42—43° after crystallisation from light petroleum (Hofmann, *J. Amer. Chem. Soc.*, 1944, **66**, 51, gives m. p. 42—43°) (Found: C, 64·4; H, 7·3. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2%). The *amide*, plates from very dilute alcohol, melted at 116—117° (Found: N, 8·1. $C_9H_{13}O_2N$ requires N, 8·4%). (*b*) β-2-Furylacraldehyde, malonic acid, pyridine, and piperidine acetate gave 4-2′-furylbuta-1 : 3-diene-1 : 1-dicarboxylic acid (53%), m. p. 190—195° (decomp.). Hofmann (*loc. cit.*) gives m. p. 190—195°. The dipotassium salt of this acid was reduced with hydrogen and palladised strontium carbonate to a syrup which, on decarboxylation in pyridine, gave δ-2-furylvaleric acid, m. p. 42—43°. (*c*) 5-2′-Furylpent-2-enoic acid was reduced in aqueous potassium hydroxide with hydrogen (Pd–$SrCO_3$) in 1 hour, giving a 73% yield of needles, m. p. 42—43°. (*d*) 1-2′-Furyl-3-iodopropane and ethyl sodiomalonate gave diethyl 4-2′-furylbutane-1 : 1-dicarboxylate, b. p. 105—112°/0·1 mm. Hydrolysis and decarboxylation at 100°/15 mm. gave the valeric acid, b. p. 120—130°/0·1 mm., m. p. 42—43°.

6-2′-*Furylhexanoic acid*. (*a*) 5-2′-Furylpentyl cyanide, hydrolysed for 42 hours in aqueous-alcoholic potassium hydroxide, gave a pale yellow oil which was taken up in ether. The ethereal solution, shaken with N-sodium carbonate solution and then acidified at 0°, gave an *acid*, b. p. 160—180°/0·01 mm., m. p. 18—19°, n_D^{20} 1·4779, d_4^{20} 1·080, $[R_L]_D^{20}$ 47·75 (calc.: 48·42) (Found: C, 65·5; H, 8·0. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·8%). The *amide*, colourless plates from aqueous ethanol, melted at 81—82° (Found: N, 7·5. $C_{10}H_{15}O_2N$ requires N, 7·7%). (*b*) To the Grignard reagent from 1-2′-furyl-5-iodopentane solid carbon dioxide was added, giving a 50% yield of acid, b. p. 114—116°/0·3 mm., n_D^{20} 1·4769, m. p. 18—19°.

7-2′-*Furylheptanoic acid*. (*a*) Hydrogenation of potassium 7-2′-furylhepta-2 : 4 : 6-trienoate in water (Pd–$SrCO_3$) gave the saturated *acid* which, crystallised from light petroleum, melted

at 35—36° (yield 86%) (Found : C, 67·2; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). The *amide*, lustrous plates from aqueous ethanol, melted at 96—97° (Found : N, 6·9. $C_{11}H_{17}O_2N$ requires N, 7·2%). (*b*) 1-Bromo-5-2′-furylpentane and ethyl sodiomalonate gave diethyl 6-2′-furylhexane-1 : 1-dicarboxylate (67%). Hydrolysis (68 hours) followed by decarboxylation gave needles (63%), m. p. 35—36°.

12-2′-*Furyldodecanoic acid.* 1-2′-Furyl-11-iodoundecane was converted into the nitrile, hydrolysis of which gave the *acid* in plates (from light petroleum), m. p. 41—42° (Found : C, 72·3; H, 9·9. $C_{16}H_{26}O_3$ requires C, 72·1; H, 9·8%). The *amide*, plates from aqueous ethanol, melted at 119—120° (Found : N, 5·0. $C_{16}H_{27}O_2N$ requires N, 5·3%).

1-2′-*Furyl*-3 : 3-*dimethoxyprop*-1-*ene*.—β-2-Furylacraldehyde (50 g.), dry methyl alcohol (90 c.c.), and phosphoric acid (0·4 g. of 100%) were kept for 12 hours at room temperature. After neutralisation with methyl-alcoholic sodium methoxide and addition of water, ether extracted the *acetal* (21 g., 30%), b. p. 112—114°/25 mm., n_D^{20} 1·5014 (Found : C, 64·1; H, 7·3. $C_9H_{12}O_3$ requires C, 64·3; H, 7·1%).

3 : 3-*Diethoxy*-1-2′-*furylprop*-1-*ene*.—The acraldehyde (42 g.) was dissolved in absolute ethanol (25 c.c.) containing ammonium nitrate (1·5 g.) (cf. Fischer and Baer, *Helv. Chim. Acta*, 1935, **18**, 514) and ethyl orthoformate (72 g.). After 10 minutes' refluxing the solution was filtered while hot. To the cold filtrate ether and then excess of 10% aqueous ammonia were added. There were obtained 42 g. (66%) of unsaturated *acetal*, b. p. 110—114°/22 mm., n_D^{20} 1·4973 (Found : C, 67·5; H, 8·1. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%).

1 : 1-*Dimethoxy*-3-2′-*furylpropane*.—Hydrogenation of the dimethoxypropene (above) with hydrogen at 4 atm. and room temperature (Pd–$SrCO_3$) gave, in 10 minutes, the dimethoxypropane (93%), b. p. 109°/30 mm., n_D^{20} 1·4546 (Found : C, 63·7; H, 8·6. Calc. for $C_9H_{14}O_3$: C, 63·5; H, 8·3%). Wienhaus and Leonhardi (*Chem. Abs.*, 1930, **24**, 2127) give b. p. 77°/4 mm., n_D^{20} 1·4550.

Similarly obtained, 1 : 1-*diethoxy*-3-2′-*furylpropane* had b. p. 110—115°/22 mm., n_D^{20} 1·4586. It decomposed rapidly and immediate analysis was essential (Found : C, 67·2; H, 9·1. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·2%).

β-2′-*Furylpropaldehyde*.—3-2′-Furyl-1 : 1-dimethoxypropane (8·5 g.) was rapidly hydrolysed in 30 c.c. of cold, aqueous-ethanolic hydrochloric acid (40 : 59 : 1 by vol.). After neutralisation with aqueous sodium carbonate the mixture yielded to ether β-2′-furylpropaldehyde (5·7 g., 90%), b. p. 80—85°/15 mm., n_D^{20} 1·4771 (Found : C, 67·5; H, 6·3. Calc. for $C_7H_8O_2$: C, 67·8; H, 6·5%). Wienhaus and Leonhardi (*loc. cit.*) give b. p. 59—61°/4 mm., n_D^{20} 1·4782. The diethyl acetal was similarly hydrolysed.

1-2′-*Furylpentane*.—1-2′-Furylpentan-1-ol, prepared in 72% yield by the action of *n*-butylmagnesium bromide in ether on an ethereal solution of furfuraldehyde (Paul, *Bull. Soc. chim.*, 1935, **2**, 2223), had b. p. 107—110°/15 mm., n_D^{20} 1·4752 (Found : C, 69·9; H, 8·8 Calc. for $C_9H_{14}O_2$: C, 70·0; H, 9·1%). Dehydration of this was best carried out by passing the vapour with the aid of carbon dioxide over alumina at 250—270° (Paul, *loc. cit.*); the yield was 34%. Other methods, refluxing with iodine or with copper sulphate, or stirring with phosphoric oxide, gave only tars. The olefin yielded a main fraction of b. p. 66—67°/16 mm., n_D^{20} 1·5007 (Found : C, 79·5; H, 8·9. $C_9H_{12}O$ requires C, 79·4; H, 8·9%), presumably 1-2′-*furylpent*-1-*ene*, but the position of the double bond was not determined.

The pentene (13·6 g.) in ethanol (60 c.c.) was completely hydrogenated at 4 atm. (Pd–$SrCO_3$; 1·0 g.) at room temperature. The product, b. p. 64—66°/23 mm., n_D^{20} 1·4478, was obtained in 88% yield (Found : C, 78·3; H, 10·3. Calc. for $C_9H_{14}O$: C, 78·2; H, 10·2%). Normant (*Ann. Chim.*, 1942, **17**, 335) gives n_D^{19} 1·4482. This furylpentane appeared to be stable to aqueous acids, but its rapid polymerisation in warm aqueous-alcoholic hydrochloric acid showed that the sparing solubility had masked the reaction.

1-(*Tetrahydro*-2′-*furyl*)*pentane*.—When 1-2′-furylpent-1-ene (41 g.) in ethanol (80 c.c.) was shaken with hydrogen at 4 atm. in presence of Raney nickel (Mozingo, *Org. Synth.*, 1941, **21**, 15) rapid absorption occurred during 8 minutes, followed by slower reduction, complete in 2 hours. The product gave a main fraction of tetrahydrofurylpentane, b. p. 78—80°/20 mm., n_D^{20} 1·4326 (30·5 g., 75%) (Found : C, 75·6; H, 12·6. Calc. for $C_9H_{18}O$: C, 76·0; H, 12·8%). Paul (*Bull. Soc. chim.*, 1938, **5**, 1053) gives b. p. 70—71°/14 mm., n_D^{10} 1·4362. n_D^{20} (calc.) should be approx. 1·4322.

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126. *Reactions of Iodine Pentafluoride with Inorganic Substances. Iodine Oxytrifluoride and Iodyl Fluoride.*

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The reactions of iodine pentafluoride with typical oxides, salts, and metals are described. They lead to a number of new compounds many of which are of a molecular type. A straightforward method of preparing iodine oxytrifluoride is given and the reactions involved are made clear. Thermal decomposition of this compound gives rise to the new iodyl fluoride, IO_2F; this can be reconverted into the oxytrifluoride by heating it with iodine pentafluoride. A study of some of these reactions and the physicochemical properties of iodine pentafluoride is still in progress.

Iodine pentafluoride was originally prepared by Moissan (*Compt. rend.*, 1902, **135**, 563) who made a cursory and qualitative investigation of its reactions with a large number of metals. Emeléus and Sharpe recently (*J.*, 1949, 2206) focused attention on the compound by preparing the polyhalide KIF_6, and showing the probable existence of an acid–base system in this solvent similar to that furnished by bromine trifluoride (Woolf and Emeléus, *J.*, 1949, 2865). In the same laboratory, Woolf (*J.*, 1950, 3678) showed that iodine pentafluoride reacts with antimony pentafluoride to give $SbIF_{10}$, with sulphur trioxide to give a constant-boiling mixture $IF_5,1{\cdot}17SO_3$, and with potassium metaphosphate, persulphate, and iodate to give $KPO_3,2{\cdot}3IF_5$, $K_2S_2O_8,1{\cdot}02IF_5$, and $KIO_3,0{\cdot}5IF_5$, respectively.

Our interest in the compound arose from a claim by Ruff and Braida (*Z. anorg. Chem.*, 1934, **42**, 220; *Angew. Chem.*, 1934, **47**, 48) to have obtained iodine oxytrifluoride from iodine pentafluoride in three ways: (*a*) as a by-product in the preparation of iodine pentafluoride from its elements, provided a little oxygen was present during the reaction, (*b*) by restricted addition of water to iodine pentafluoride, and (*c*) by reaction between iodine pentafluoride and iodine pentoxide. The second method did not appear likely to give a unique product or a mixture readily separable, but we gave extended trial to the first method, using, as a source of oxygen, the gas itself and also silica powder mixed with the iodine. In every case, even when considerable quantities were used, we got iodine pentafluoride which on distillation left a minute, white residue insufficient for identification. The fluorination of iodine pentoxide with fluorine diluted to various extents with nitrogen gave no better results; but iodine pentoxide dissolved in boiling iodine pentafluoride to a colourless solution which, on cooling to room temperature, deposited white crystals of iodine oxytrifluoride: $I_2O_5 + 3IF_5 \longrightarrow 5IOF_3$. This reaction Ruff and Braida believed to be reversible on heating, but this is not the case. It goes smoothly until all the oxide is consumed, the oxy-compound dissolving in the excess of pentafluoride. Actually, on heating the oxytrifluoride at 110° we observed a new reaction leading to the hitherto unrecorded iodyl fluoride, IO_2F: $2IOF_3 \rightleftarrows IO_2F + IF_5$. This is an interesting change because it is reversible. When iodyl fluoride is refluxed with iodine pentafluoride it goes completely into solution, and the oxytrifluoride is recovered. The forward reaction possibly has more than a formal resemblance to the decomposition of $K^+(IF_6)^- \longrightarrow KF^+ + IF_5^-$, for it may well be that iodine oxyfluoride has the form $(IO_2)^+(IF_6)^-$ of an ionic compound.

The new iodyl fluoride is a white solid, stable in dry air, not appreciably hygroscopic but slowly evolving hydrogen fluoride on exposure to moist air. It readily dissolves in water with irreversible hydrolysis to iodic and hydrofluoric acids: $IO_2F + H_2O \longrightarrow HIO_3 + HF$. At about 220° iodyl fluoride attacks glass and iodine is liberated.

Iodine dioxide, I_2O_4, also dissolves in iodine pentafluoride with formation of the oxytrifluoride contaminated with some free iodine. In this preparation, and in that of iodine pentafluoride from its elements, the iodine pentafluoride assumes a bright blue colour, similar in shade to a dilute solution of tetramminocupric salt and quite unlike that of iodine itself in any solvent. This was casually mentioned by Ruff and Braida (*loc. cit.*). We have found that it is not due to iodine itself, which when added to iodine pentafluoride gives a chocolate-brown solution. From such a solution, however, it can be formed by addition of a certain amount of fluorine, but the colour is discharged by the slightest excess of fluorine

beyond that point: efforts to concentrate it have been unsuccessful. We incline to the view that it is a lower fluoride of iodine, subject to autoxidation even at very moderate concentrations to the pentafluoride, and completely obscured by the presence of traces of free iodine. We think it may be iodine trifluoride, IF_3, and that it may form an intermediate stage in fluorination to the pentafluoride, just as that compound is a step on the road to the heptafluoride.

We have also found that phosphorus and vanadium pentoxides, and chromium and tungsten trioxide dissolve freely in hot iodine pentafluoride, and we have isolated POF_3, VOF_3, CrO_2F_2, and $WO_3,2IF_5$ respectively, from these reactions. Molybdenum trioxide proved to be less soluble and gave $2MoO_3,3IF_5$, whereas arsenic pentoxide was insoluble; but the latter takes up iodine pentafluoride to give a bulky white solid of indefinite composition. Although antimony pentoxide dissolved freely, the residue left after evaporation required to be heated to 170° under reduced pressure before the last traces of solvent were removed: the final residue corresponded to SbF_5,IO_2F.

Neither carbon monoxide nor sulphur dioxide reacted with iodine pentafluoride, but nitrogen dioxide dissolved readily and the solution yielded a deep cream-coloured, crystalline solid IF_5,NO_2. This compound sublimes unchanged when gently heated, but higher temperatures lead to its decomposition with liberation of nitrogen dioxide. It evidently has a slight vapour pressure of NO_2 for the presence of that gas is discerned after the material has been sealed in an evacuated tube for some time. Dilute potassium hydroxide rapidly attacks it with formation of iodate and fluoride ions and liberation of some brown fumes.

As mentioned above, Woolf (*loc. cit.*) showed that certain salts, both those insoluble and those soluble in that liquid, form addition compounds with iodine pentafluoride. We have shown that potassium periodate freely dissolves in boiling iodine pentafluoride without trace of decomposition and that the solution deposits colourless, cubic crystals of KIO_4,IF_5 on cooling. The reaction of the liquid with nitrates is very selective. For instance, potassium nitrate is decomposed by boiling iodine pentafluoride which expels the acid radical—brown fumes may be seen—and converts the whole of the potassium into the iodohexafluoride, KIF_6, first isolated by Emeléus and Sharpe (*loc. cit.*). Barium and silver nitrates, on the other hand, were insoluble but both retained some pentafluoride in the residues recovered, $Ba(NO_3)_2,2{\cdot}5IF_5$ and $AgNO_3,0{\cdot}1IF_5$.

We did not expect any reaction with the more noble metals and, indeed, silver was untouched, but following up Moissan's observation (*loc. cit.*) of a slight attack on mercury, we have found that that metal is slowly dissolved, with separation of a light brown solid $Hg(IF_5)_2$. This substance changes slowly from buff to red on exposure to air; in water it does not dissolve but slowly hydrolyses; in sodium hydroxide solution decomposition is rapid and results in a precipitate of yellow mercuric oxide and a solution containing iodate and fluoride ions. Metallic cadmium by contrast is converted into fluoride with the consequent liberation of iodine.

Experimental

Iodine Oxytrifluoride.—About 10 g. of iodine pentafluoride, prepared by burning dry iodine in fluorine–nitrogen (40 : 60, by vol.), was fractionated in a vacuum to free it from fluorine and heptafluoride, and was condensed, under the same conditions, on to 0·25 g. of iodine pentoxide. Dry nitrogen was admitted to atmospheric pressure and the mixture was heated to its b. p. When saturated with pentoxide, the solution was separated from the residue, which was filtered off through a sintered-glass filter incorporated in the apparatus. When the clear, colourless solution was cooled, white needles of *iodine oxytrifluoride* separated. The mother-liquor was removed by decantation, and the excess of iodine pentafluoride under vacuum at room temperature (1½ hr.) (Found: I, 64·0; F, 28·0. IOF_3 requires I, 63·6; F, 28·5%).

Iodyl Fluoride.—Iodine oxytrifluoride, when heated to 110° in the presence of dry nitrogen, fell to a white powder, and elsewhere in the apparatus iodine pentafluoride collected. To remove the last trace of the latter, the solid was kept at 110°, the vessel being subjected to continuous exhaustion, for an hour. The residual *iodyl fluoride* was a fine white powder (Found: I, 71·0; F, 10·75. IO_2F requires I, 71·3; F, 10·7%).

Iodyl fluoride (1 g.) when refluxed with iodine pentafluoride for several hours, dissolved to a

colourless solution which, on cooling, deposited white, needles. The excess of iodine pentafluoride was removed by pouring off and by prolonged pumping at room temperature. The crystals were iodine oxytrifluoride (Found: I, 63·1; F, 28·3%).

When heated to 220°, iodyl fluoride loses iodine and considerably attacks glass. It is not appreciably hygroscopic, but on long storage in moist air hydrogen fluoride is slowly evolved. Water readily and quietly dissolves it to form iodic and hydrofluoric acids; and sodium hydroxide solution converts it into the alkali iodate and fluoride. When the solid is added to silver nitrate solution, silver iodate is precipitated and silver fluoride left in solution. Iodyl fluoride does not attack boiling chloroform or carbon tetrachloride; it darkens pyridine slightly and liberates iodine in contact with acetyl chloride at temperatures as low as −15°.

Reactions of Iodine Pentafluoride with Oxides.—Nitrogen dioxide. Nitrogen dioxide was absorbed at the surface of liquid iodine pentafluoride, which became first pale and then deep yellow. A solid began to crystallise on the walls of the vessel and, with the continued passage of gas, the liquid was almost completely converted into a solid. The current of nitrogen dioxide was stopped, the excess of iodine pentafluoride pumped off, and the solid dried at 100°, forming a deep cream-coloured, granular powder. It was the molecular *compound* IF_5,NO_2 (Found: I, 47·6; F, 34·6; NO_2, 17·6. IF_5,NO_2 requires I, 47·4; F, 35·4; NO_2, 17·2%). The compound sublimed when gently heated but decomposed at higher temperatures, liberating nitrogen dioxide. It had a distinct vapour pressure of nitrogen dioxide at room temperature for, on storage for a few weeks in a sealed glass tube under a vacuum, brown fumes appeared. Dilute potassium hydroxide reacted vigorously with it to form iodate and fluoride, some of the nitrogen dioxide escaping even through the alkaline solution. For analysis, the tube containing the compound had to be broken in a stoppered bottle containing the alkali.

Phosphoric oxide. Phosphoric oxide (0·15 g.) in iodine pentafluoride (10 g.) showed no change at room temperature but dissolved on gentle warming to a clear, colourless solution. No gas was evolved. On cooling, no solid separated until some of the iodine pentafluoride had been evaporated (at 5 mm. pressure). This solid, a fine white powder, proved to be iodine oxytrifluoride contaminated with a small amount of a phosphorus compound (Found: I, 59·2; F, 26·95; P, 1·80; total, 97·95%; I : F = 1 : 3·03). If, as is possible, the contaminant was phosphorus oxytrifluoride, the phosphorusf ound would indicate that it was present to the extent of about 6%. Allowance for this would require I, 59·7; F, 26·8%, in good agreement with the analytical results.

The liquid distillate was unchanged iodine pentafluoride with about 98·2% of the phosphorus originally present. We believe that the oxytrifluorides of both phosphorus and iodine are formed in accordance with the reaction: $P_2O_5 + 3IF_5 \longrightarrow 2POF_3 + 3IOF_3$. Although phosphorus oxytrifluoride is a gas (b. p. −38·8°) it remained in solution in the iodine pentafluoride, possibly, like vanadium (see below), forming a weakly linked molecular compound of POF_3 and IF_5 stable only in solution. When the mixture is distilled under reduced pressure, the compound is decomposed, giving a distillate of phosphorus oxytrifluoride dissolved in iodine pentafluoride and leaving a residue of solid iodine oxytrifluoride contaminated with a few units % of phosphorus oxytrifluoride.

Vanadium pentoxide. The oxide (0·2 g.), refluxed with iodine pentafluoride (10 g.) for 1 hour, gave a colourless solution which, on cooling, deposited a light yellow solid. The excess of pentafluoride was removed at 20°/3 mm. until the *complex* attained a constant weight (Found: V, 11·9; I, 45·9; F, 33·0. $2VOF_3,3IOF_3$ requires V, 12·0; I, 44·9; F, 33·6%).

Arsenic pentoxide. This solid increased appreciably in bulk when refluxed with iodine pentafluoride, but little of it appeared to dissolve. The residue from different experiments was far from constant in composition (Found, in two samples: As, 35·6, 20·6; I, 35·1, 40·9; F, 9·8, 10·5%).

Antimony pentoxide. The oxide (0·08 g.) slowly dissolved in hot iodine pentafluoride (10 g.). A temperature of 170° was necessary to remove the last traces of solvent, at which temperature the product appeared to be molten. On cooling it set to an opaque yellow solid *complex* (Found: Sb, 16·4; I, 50·9; F, 19·8. $SbF_5,3IO_2F$ requires Sb, 16·2; I, 50·7; F, 20·2%).

Molybdenum trioxide. The oxide did not dissolve but increased in bulk. After removal of the iodine pentafluoride, a white *complex* remained (Found: Mo, 21·5; I, 39·4; F, 28·6. $2MoO_3,3IF_5$ requires Mo, 20·3; I, 39·9; F, 29·9%).

Tungsten trioxide. Tungstic oxide dissolved easily in boiling iodine pentafluoride to give a slightly opalescent solution. When excess of the solvent was removed there remained a light yellow solid the composition of which moved towards $WO_3,2IF_5$ as a limit, as the temperature was raised: at 50°, 70°, 100°, and 160°, IF_5/WO_3 = 3·1, 2·6, 2·2, and 2·1, respectively. Al-

though it appears that the compound at 160° was $WO_3,2IF_5$, it always had an excess of iodine (Found: W, 26·2; I, 41·8. $WO_3,2IF_5$ requires W, 27·2; I, 37·6%).

Chromium trioxide. Iodine pentafluoride (2 g.), heated at 100° in a sealed tube with excess of chromium trioxide, gave a reddish, volatile product which, when separated from other volatile material by repeated fractional distillation, proved to be chromyl fluoride (Found: Cr, 43·3; F, 33·0. Calc. for CrO_2F_2: Cr, 42·6; F, 31·2%).

Reactions of Iodine Pentafluoride with Salts.—Potassium iodate. The salt (0·5 g.) readily dissolved in iodine pentafluoride (12 g.). After removal of excess of the latter at room temperature, and then at 120° under a vacuum, the viscous mass yielded a white *compound* KIO_4,IF_5 (Found: K, 8·7; I, 55·0; F, 20·9. KIO_4,IF_5 requires K, 8·6; I, 56·2; F, 21·0%).

Potassium nitrate. Potassium nitrate (0·5 g.), when boiled with iodine pentafluoride (10 g.), evolved nitrogen dioxide. The solution remaining at the end of the reaction gave, after removal of iodine pentafluoride under a vacuum at 20°, a white powder, KIF_6 (Found: K, 13·1; I, 44·5; F, 40·4. Calc. for KIF_6: K, 13·9; I, 45·4; F, 40·7%).

Barium nitrate. Barium nitrate (0·4 g.), refluxed with iodine pentafluoride (10 g.) for 3 hours, gave no nitrogen dioxide but increased in bulk. Removal of the excess of iodine pentafluoride, at 5 mm. and room temperature, left a white solid; the increase in weight suggested formation of the *compound* $Ba(NO_3)_2,2{\cdot}5IF_5$ [Found: Ba, 16·0; N, 3·7. $Ba(NO_3)_2,2{\cdot}5IF_5$ requires Ba, 16·8; N, 3·4%].

Reaction of Iodine Pentafluoride with Mercury.—Mercury (0·15 g.), covered with iodine pentafluoride (*ca.* 10 g.) and kept at room temperature for 24 hours, developed a thin film of white solid on its surface. When heated to boiling and refluxed with frequent shaking for 5 hours, all the mercury was converted into a dense white solid. When the liquid was removed, first at 3 mm. and then by heating at 100° for a few minutes, the solid *compound* became light brown [Found: Hg, 30·6; I, 39·4; F, 29·9. $Hg(IF_5)_2$ requires Hg, 31·1; I, 39·4; F, 29·5%], and when left in the air it became red. It appeared to be insoluble in water, but after some days the liquid was decidedly acid, suggesting hydrolysis. The compound was soluble in alcohol but insoluble in chloroform, which was, however, coloured slightly purple, indicating that the pale brown colour was possibly due to a trace of free iodine. With sodium hydroxide the compound was rapidly hydrolysed, iodate and fluoride being formed in solution, and the mercury being quantitatively precipitated as yellow oxide.

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KING'S COLLEGE, NEWCASTLE-ON-TYNE. [*Received, October 31st*, 1952.]

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127. *The Characteristic Infra-red Absorption of Some Organic Derivatives of Phosphoric Acid.*

By M. HALMANN and S. PINCHAS.

The infra-red spectra of a number of mixed organic phosphates, dialkyl chlorophosphonates, and dialkyl alkylaminophosphonates were measured in the 1060—900 cm.$^{-1}$ region. They all show the characteristic absorption bands of the simple trialkyl phosphates, usually accompanied by some other bands.

IN a previous communication (Bergmann, Littauer, and Pinchas, *J.*, 1952, 847), it was shown that various trialkyl phosphates show two strong bands in the 1060—900 cm.$^{-1}$ region, at about 1040—1030 and 970—1000 cm.$^{-1}$. These were assigned to the P–OR stretching modes of vibration and it was assumed that the 1030-cm.$^{-1}$ band is due to the out-of-phase stretching of the three alkoxy-groups, while that of 970 cm.$^{-1}$ belongs to the more symmetrical in-phase stretching. It was therefore interesting to see whether the less symmetrical mixed trialkyl phosphates also show these characteristic bands at the same places, and equally whether the dialkyl chlorophosphonates which contain only two alkoxy-groups bound to the phosphorus atom, and contain in addition the heavy and negative chlorine atom, have their P–OR stretching bands at the same frequencies.

In spite of the seemingly large differences between the dialkyl chlorophosphonates and the trialkyl phosphates, such an analogy could be expected in the light of the fact that many

similar compounds of the general structure $R{\cdot}PO(OR')_2$, where R and R′ are alkyl groups, show strong bands at about the same frequencies (Meyrick and Thompson, *J.*, **1950**, 225; Daasch and Smith, *Analyt. Chem.*, 1951, **23**, 853), and that even in the case of the negatively substituted diethyl fluorophosphonate two strong bands appear at about **1040** and **980** cm.$^{-1}$ (Daasch and Smith, *loc. cit.*). Of the dialkyl chlorophosphonates, however, only the diethyl chlorophosphonate seems to have been measured (Gore, *Discuss. Faraday Soc.*, **1950**, **9**, 138) and indeed it showed bands at about **1030**, **990**, and **970** cm.$^{-1}$ (read from the curve). Some diethyl phenyl phosphates have been investigated, all of them showing strong bands at about **1060—1040** and **970** cm.$^{-1}$ in addition to some other bands (*loc. cit.*), but no simple mixed phosphates seem to have been measured. Table 1 summarises some of our measurements for a number of mixed alkyl phosphates and chlorophosphonates.

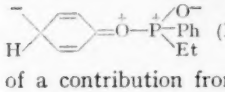
TABLE 1. *Infra-red absorption of mixed organic phosphates and dialkyl chlorophosphonates in the* **1060—900** *cm.*$^{-1}$ *region.*

(Solvent: 1 c.c. of carbon tetrachloride.)

No.	Substance	G.	Cell thickness, mm.	Absorption bands (cm.$^{-1}$)
1	$PO(OEt)(OMe)_2$	0·042	0·1	**1036** (broad; strongest), **968**
2	$PO(OEt)(OPr^i)_2$	0·016	0·1	**1059**, **1005** (strongest), **899** [a] (very weak)
3	$PO(OEt)(OPh)_2$	0·030	0·1	**1043**, **1025**, **1006**, **952** (strongest)
4	$Cl{\cdot}PO(OMe)_2$	(0·25 c.c.)	0·03	**1037** (strongest), **969**
5	$Cl{\cdot}PO(OEt)_2$	0·019	0·1	**1043** (strongest), **1010**, **979**
6	$Cl{\cdot}PO(OPr^i)_2$	(0·25 c.c.)	0·03	**997** (strongest), **930** (shoulder) [a]
7	$Cl{\cdot}PO(OPh)_2$	0·051	0·1	**1025** (s), **1010**, **999**, **962** (strongest), **930** (shoulder)

[a] Probably an *iso*propyl-group absorption.

If the results for the mixed phosphates are compared with those obtained for the corresponding normal phosphates, *viz.*, trimethyl phosphate **1043** (s), tri*iso*propyl phosphate **995** (s), **931** (very weak) (Bergmann, Littauer, and Pinchas, *loc. cit.*), triphenyl phosphate **1060**, **1030**, **1010** (s), **960** (very strong) (Daasch and Smith, *loc. cit.*), it can be seen that the characteristic phosphate bands are remarkably steady and are only very little affected by the destruction of the high symmetry of the homogeneous phosphates. (The small dissymmetry which may be introduced by free rotation along the C–O bonds probably cannot bring about marked differences in the P–OC frequencies of the ensuing rotational isomers and *this* dissymmetry can therefore be overlooked as far as the P–OC frequencies are concerned.) This loss of symmetry, as could be expected, brings about, however, an additional band in this region (**968** cm.$^{-1}$ in No. 1, **1059** cm.$^{-1}$ in No. 2; in No. 3 it may be concealed by the numerous bands already existing). It can further be seen that the merging together of the two phosphate bands which occurs in tri*iso*propyl phosphate takes place also in ethyl di*iso*propyl phosphate; it seems, further, that the additional **1059** cm.$^{-1}$ band is due to that mode of vibration in which the stretching of the P–OEt bond is not in phase with that of the two *iso*propoxy-groups (as the value of ε_{1059} is as high as **400**, it is improbable that it is an ordinary ethyl absorption). The in-phase stretching, as well as that in which one *iso*propoxy-group is out of phase, appears to remain more or less as in tri*iso*propyl phosphate. In ethyl dimethyl phosphate the presence of the **968** cm.$^{-1}$ band is noteworthy, since in the more symmetrical methyl phosphate and methyl pyrophosphate it is absent (Bergmann, Littauer, and Pinchas, *loc. cit.*). Another band is possibly concealed in the high-frequency side of the broad **1038** cm.$^{-1}$ band. Of the four bands of ethyl diphenyl phosphate, some seem to be due to the monosubstituted benzene (cf. Colthup's table, *J. Opt. Soc. Amer.*, **1950**, **40**, 397) and the additional P–OEt stretching. The two characteristic phosphate bands appear to be shifted from the usual **1030—1040** cm.$^{-1}$ and **970—1000** cm.$^{-1}$ frequencies to **1006** and **952** cm.$^{-1}$, respectively, with the relative intensity also changed in favour of the latter. Such is also the case in triphenyl phosphate (Daasch and Smith, *loc. cit.*), in diphenyl chlorophosphonate (Table 1, No. 7), and in diphenyl di-*n*-butylaminophosphonate (Table 2, No. 5). It seems that this lowering of the P–OR frequencies reflects a weakening of the P–$OC_{ar.}$ bond as compared with a P–$OC_{aliph.}$ bond, possibly because of a contribution from resonating structures such as (I) to the actual state of phenyl phosphates (mutual electrostatic repulsion between P–O tending to rupture the bond).


(I)

Examination of the results for the dialkyl chlorophosphonates reveals that here also the characteristic phosphate bands appear always at about the same frequencies as in the corresponding trialkyl phosphates, thus proving anew the validity of their assignments. The interesting conclusion which emerges, *viz.*, that the additional alkoxy-group in trialkyl phosphates does not change appreciably the characteristic absorption of the system $\cdot PO(O \cdot C_nH_m)_2$ existing in the chlorophosphonates (and, of course, in the various phosphonates studied by Meyrick and Thompson, *loc. cit.*) has its immediate analogy in the acetals and ortho-esters (Bergmann, Bograchov, and Pinchas, *J. Amer. Chem. Soc.*, 1951, **73**, 2352). In this connection it is noteworthy that even a system (which contains one P–OC bond only) like that of $PO(SEt)_2(OEt)$, also has two strong bands at about 1030 cm.$^{-1}$ and 950 cm.$^{-1}$ (Gore, *loc. cit.*).

The presence of the 969-cm.$^{-1}$ band in dimethyl chlorophosphonate is again (cf. No. 1, 968 cm.$^{-1}$) noteworthy, the more so because dimethyl fluorophosphonate (Daasch and Smith, *loc. cit.*) lacks this band for some unknown reason. The absorption bands of diethyl chlorophosphonate are in perfect agreement with those of ethyl phosphate (Bergmann, Littauer, and Pinchas, *loc. cit.*), *viz.*, 1036 and 974 cm.$^{-1}$, the additional band at 1010 cm.$^{-1}$ being probably due to some other mode of vibration; their values as measured by us are, however, somewhat different from those read from Gore's curve (*loc. cit.*). In di*iso*propyl chlorophosphonate we find once more the two characteristic bands merged together under the influence of the branched alkyl groups. Diphenyl chlorophosphonate, finally, shows great similarity to the absorption of the triphenyl phosphate as quoted above.

In view of the great likeness, as far as the molecular spectra are concerned, between an oxygen and a nitrogen atom, especially when bound to a hydrogen atom (*e.g.*, dibutyl ether and dibutylamine have similar infra-red spectra—see curves Nos. 126 and 238, Barnes, Gore, Liddel, and Williams, " Infra-red Spectroscopy," New York, 1944), it was interesting to see whether the dialkyl alkylaminophosphonates would show the characteristic absorption of the tri-esters. As Table 2 shows, this is the case.

The phosphate bands appear in all the substances but are usually shifted towards the longer wave-lengths (especially the second band) and are often accompanied by more bands because of their lower symmetry. This shift seems to suggest that the P–NC bond is weaker than the P–OC bond, which is to be expected. [Although no data seem to be available for the relative strengths of these two bonds we can assume them to be parallel to those of the di-atoms PO and PN, respectively, for which Linnett (*Trans. Faraday Soc.*, 1942, **38**, 1) calculated the heats of dissociation to be 14·75 and 7·81 *A.* erg/molecule, respectively.] All the di*iso*propyl esters in Table 2 seem to regain the normal double (or multiple) character of the phosphate bands under the influence of the substituted amino-group; the dimethyl derivative (No. 2), however, retains its singularity of not showing the

TABLE 2. *Infra-red absorption of dialkyl aminophosphonates in the* 1060—900 *cm.*$^{-1}$ *region.*

(Solvent: 1 c.c. of carbon tetrachloride; 0·1 mm. cell thickness.)

No.	Substance	G.	Absorption bands (cm.$^{-1}$)
1	$NHBu \cdot PO(OPr^i)_2$	0·015	1011, 984 (strongest), 894 [a]
2	$NBu_2 \cdot PO(OMe)_2$	0·019	1032 (strongest), 926 (weak)
3	$NBu_2 \cdot PO(OEt)_2$	0·016	1031 (strongest), 956, 938
4	$NBu_2 \cdot PO(OPr^i)_2$	0·016	1006, 979 (strongest), 929 [a]
5	$NBu_2 \cdot PO(OPh)_2$	0·022	1059, 1022, 920 (strongest)
6	$NHPh \cdot PO(OPr^i)_2$	0·040	1031 (shoulder), 1011, 990 (strongest), 958, 932 [a]
7 [b]	$PO(OEt)_3$	0·043	1036 (strongest), 974

[a] Probably an *iso*propyl-group absorption. [b] For comparison (see Bergmann *et al.*, *loc. cit.*).

second band (970—1000 cm.$^{-1}$; the 926-cm.$^{-1}$ band seems to be additional) in spite of the destruction of the high symmetry of the tri-ester. Noteworthy is the large shift in the frequency of the second band of the diphenyl derivative (No. 5) as a result of the superposition of the two effects mentioned, *viz.*, that of the phenyl group and that of the P–NC bond.

Experimental

The instrument used for the infra-red measurements has already been described (Bergmann *et al.*, *loc. cit.*) The dialkyl chlorophosphonates were obtained by chlorination of the corresponding dialkyl hydrogen phosphites (McCombie, Saunders, and Stacey, *J.*, 1945, 380), purified by vacuum distillation, and identified by chlorine determination. Diphenyl chlorophosphonate, prepared from phosphorus oxychloride and phenol (Brigl and Mueller, *Ber.*, 1939, **72**, 2121), had b. p. 150—153°/1 mm.

The following phosphate esters $PO(OR)_2(OEt)$ and aminophosphonate esters $NR'R''\cdot PO(OR)_2$ were synthesised from the corresponding chlorophosphonate $Cl\cdot PO(OR)_2$ by reaction with ethanol and the appropriate amine, respectively (details will be published separately): Ethyl dimethyl phosphate, b. p. 112—113°/41 mm., n_D^{22} 1·3984 (prepared by Drushel, *Amer. J. Sci.*, 1918, **43**, 57); ethyl di*iso*propyl phosphate, b. p. 110—112°/23 mm., n_D^{25} 1·4044, d_{25}^{25} 1·0066; ethyl diphenyl phosphate, b. p. 181—185°/2 mm., n_D^{30} 1·5250, d_{25}^{25} 1·185 (see Morel, *Compt. rend.*, 1898, **127**, 1024; 1899, **128**, 508; *Bull. Soc. chim.*, 1899, **21**, 492); dimethyl di-*n*-butylaminophosphonate, b. p. 81—82°/0·5 mm., n_D^{25} 1·4327; diethyl di-*n*-butylaminophosphonate, b. p. 93—100°/0·5 mm., n_D^{25} 1·4299; di*iso*propyl di-*n*-butylaminophosphonate, b. p. 110—112°/2 mm., n_D^{25} 1·4272; di*iso*propyl *n*-butylaminophosphonate, b. p. 99—101°/0·5 mm., n_D^{25} 1·4239; di*iso*propyl anilinophosphonate, m. p. 120° (McCombie *et al.*, *loc. cit.*); diphenyl di-*n*-butylaminophosphonate, b. p. 190—200°/2 mm., b. p. 170—173°/0·5 mm., n_D^{25} 1·5173.

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128. *Low-temperature Photochromism and its Relation to Thermochromism.*

By Yehuda Hirshberg and Ernst Fischer.

When solutions of dianthrone, dixanthylen, xanthylideneanthrone, and their derivatives are irradiated at temperatures between −70° and −150° with light of wave-length not exceeding 450 mμ, reversible formation of coloured modifications takes place (photochromism). Comparison of the visible and near ultra-violet absorption spectra of these coloured modifications with the spectra of the coloured forms obtained reversibly on heating solutions of some of the above compounds (thermochromism) shows that the colours produced by both processes are identical, and that low-temperature irradiation may cause considerable or even complete conversion into the coloured form.

Photochromism is also observed with non-thermochromic derivatives of the above compounds.

From the temperature dependence of the rates of the spontaneous disappearance of colour, the critical increments and frequency factors of the thermal reversion to the colourless modification were estimated.

The dielectric constant of solutions of xanthylideneanthrone in toluene at −78° increased considerably as a result of irradiation.

The relation between photochromism and thermochromism is discussed, and tentative conclusions are drawn with regard to the mechanism of photochromism and the electronic and atomic configuration of the coloured and colourless modifications.

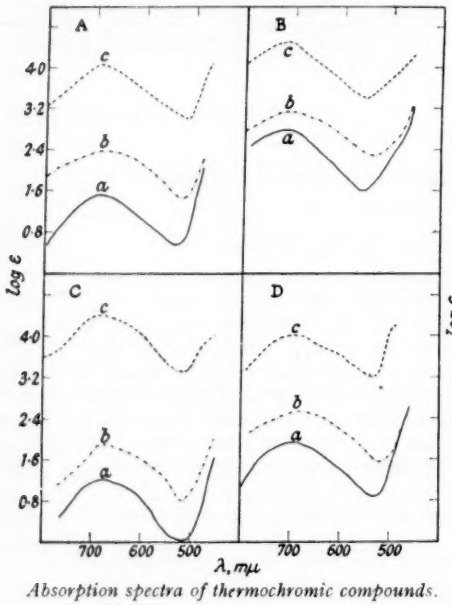
The reversible formation of colour on heating of solutions of dianthrone (dianthronylidene) (I), dixanthylen (dixanthylidene) (II), xanthylideneanthrone (III), and their derivatives is well-known (for refs. see E. D. Bergmann, "Isomerism and Isomerisation," Interscience Publishers Inc., New York, 1948; Grubb and Kistiakowsky, *J. Amer. Chem. Soc.*, 1950, **72**, 419). Theilacker, Kortüm, and Friedheim (*Ber.*, 1950, **83**, 508) and Grubb and Kistiakowsky (*loc. cit.*) measured the molar extinction coefficient (ε) of (I) and (II) at several temperatures, and concluded that thermochromism involves transition from a singlet to a diradical triplet state, the reverse transition requiring activation energies below 20 kcal./mole. Theilacker *et al.* also postulated a thermal equilibrium between two interconvertible modifications, and from a plot of log $\varepsilon_{max.}$ (*i.e.*, the value of ε at the peak of the absorption curve in the visible range) against the reciprocal of the absolute temperature

(1/T) found that the heats of conversion into the coloured form are 3·5—5 kcal./mole. Assuming that at infinite temperature this conversion is virtually complete, they estimated the $\varepsilon^{\infty}_{max.}$ of the pure coloured form by extrapolating the above plot to $1/T = 0$.* Values of log $\varepsilon^{\infty}_{max.} = 3{\cdot}5$ were thus obtained for both compounds. From the ratio $\varepsilon_{max.}/\varepsilon^{\infty}_{max.}$ the degree of conversion into the coloured form was calculated for each temperature.

In a preliminary note, Hirshberg (*Compt. rend.*, 1950, **231**, 903) reported that certain derivatives of dianthrone are reversibly converted into coloured modifications by irradiation at low temperatures.† This phenomenon (photochromism) is now described in detail, and its relation to thermochromism elaborated. Similar observations with some spirans have already been reported (*J.*, 1952, 4522).

FIG. 1.

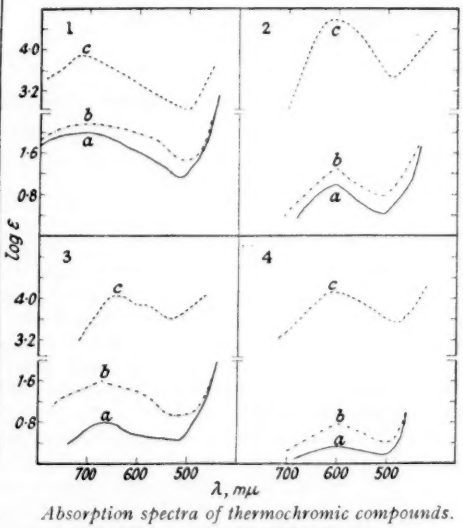
A. 2 : 2′-*Dibromodianthrone.*
B. 2 : 2′-*Dimethoxydianthrone.*
C. *Dianthrone.*
D. 2 : 2′-*Dimethyldianthrone.*



Absorption spectra of thermochromic compounds.
(*a*) *At* 298° K.
(*b*) *At* 418° K.
(*c*) *After low-temperature irradiation.*

FIG. 2.

1. *Xanthylideneanthrone.*
2. 4 : 4′-*Dimethoxydixanthylen.*
3. 3 : 3′-*Dibromodianthrone.*
4. *Dixanthylen.*



Absorption spectra of thermochromic compounds.
1. (*a*) *At* 363° K. (*b*) *At* 408° K. } (*c*) *After low-temperature irradiation.*
2. (*a*) *At* 418. (*b*) *At* 458.
3. (*a*) *At* 298. (*b*) *At* 408.
4. (*a*) *At* 363. (*b*) *At* 423.

Irradiation of solutions of (I), (II), (III), and their derivatives at room temperature generally causes irreversible chemical changes of these substances (Brockmann and Muehlmann, *Ber.*, 1950, **83**, 348; Schoenberg, Ismail, and Asker, *J.*, 1946, 442), but at <*ca.* −70° [or −100° for (I), (II), and some of their derivatives], these irreversible changes are almost completely suppressed, and intense colours are reversibly produced instead. No such effect is observed with the solids or with solutions in rigid glassy media (*e.g.*, methanol–ethanol below −120°), but in solutions in *iso*pentane (m. p. −160·5°) colour is formed even at −150°. The phenomenon thus appears to occur as long as the solution is fluid. No photochromism was observed in any case when the irradiation was carried out with light of wave-length >*ca.* 450 mμ.

* This extrapolation does not seem to be justified thermodynamically, but appears to give the correct order of magnitude for $\varepsilon_{max.}$ of the pure coloured form.

† The results there reported for dianthrone were obtained at temperatures which were not sufficiently low, and should be revised in accordance with the present communication.

The absorption spectra of the coloured forms of the above substances are recorded in Figs. 1, 2, and 3 (broken curves). In all cases the solutions were irradiated until there was no further increase in absorption intensity. No appreciable difference in $\varepsilon_{max.}$ was found between solutions in alcohol and in *iso*heptane.

The irradiated solutions lose their colour at rates depending on their temperature, and the production and loss of colour may be repeated indefinitely. The rates of these spontaneous reversion reactions were measured for each compound at several temperatures. The reactions being assumed to be of first order, their critical increments were estimated from the slopes of the graphs of reversion time against $1/T$ (Fig. 4). From the resulting

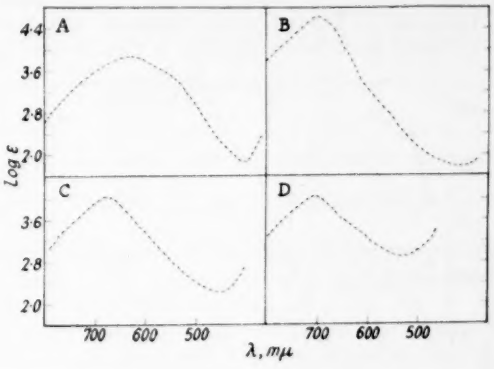


FIG. 3. *Absorption spectra of non-thermochromic compounds, after low-temperature irradiation.*

A. 4 : 4′-*Dimethyldianthrone.*
B. 4 : 4′-*Dimethoxydianthrone.*
C. 4 : 4′-*Dibromodianthrone.*
D. 3 : 4-3′ : 4′-*Dibenzodianthrone.*

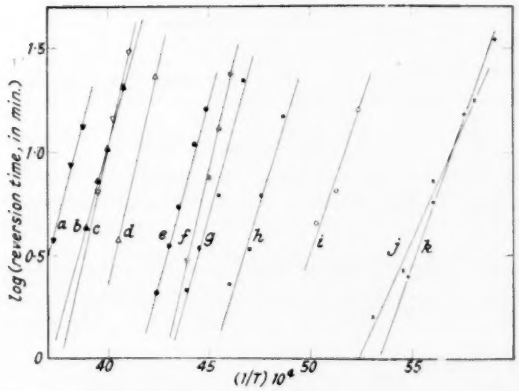
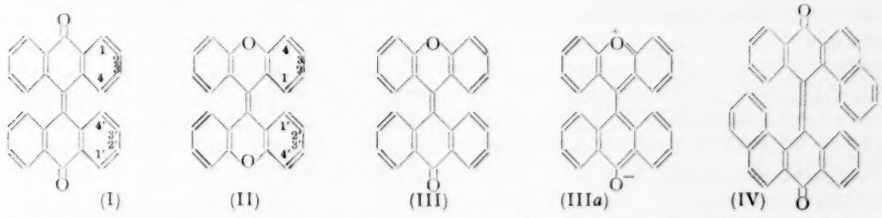


FIG. 4. *Temperature dependence of rate of colour disappearance.*

(*a*) 2 : 2′-*Dimethoxydianthrone.*
(*b*) 2 : 2′-*Dimethyldianthrone.*
(*c*) 2 : 2′-*Dibromodianthrone.*
(*d*) 3 : 3′-*Dibromodianthrone.*
(*e*) 4 : 4′-*Dimethyldianthrone.*
(*f*) *Xanthylideneanthrone.*
(*g*) 3 : 4-3′ : 4′-*Dibenzodianthrone.*
(*h*) 4 : 4′-*Dibromodianthrone.*
(*i*) 4 : 4′-*Dimethoxydianthrone.*
(*j*) 4 : 4′-*Dimethoxydixanthylen.*
(*k*) *Dixanthylen.*

values and the actual rates of reaction, the frequency factors A were evaluated and are listed in Table 1, together with the critical increments, for all the compounds investigated.

The photochromic substances listed in group (*b*) of Table 1 also show thermochromic behaviour. The absorption spectra of dimethyl phthalate solutions of these substances



at room temperature and at higher temperatures are shown in Figs. 1 and 2. By following the method of Theilacker *et al.* (*loc. cit.*), the energy difference ΔH between the coloured

and colourless forms, the values of $\varepsilon^{\infty}_{max.}$ (see p. 631), and the degree of conversion into the coloured form at each temperature were calculated (Tables 1 and 2).

Comparison of the absorption spectra of the thermochromic and photochromic coloured modifications, for the substances exhibiting both phenomena (Figs. 1 and 2), shows that the temperature-dependent band of the thermochromic coloured forms is practically identical with the visible band of the photochromic coloured modification. Moreover, inspection of cols. 4 and 5 of Table 1 shows that the thermochromic $\varepsilon^{\infty}_{max.}$ and the photochromic $\varepsilon_{max.}$ are both of an order of magnitude which may be expected by analogy with other dyes. (Values of log $\varepsilon_{max.}$ exceeding 5 are extremely rare for any type of dye.) It therefore appears plausible that the coloured modifications formed either by heat or by low-temperature irradiation are identical, and that in the latter process conversion into the coloured form takes place to a considerable extent under the conditions described.

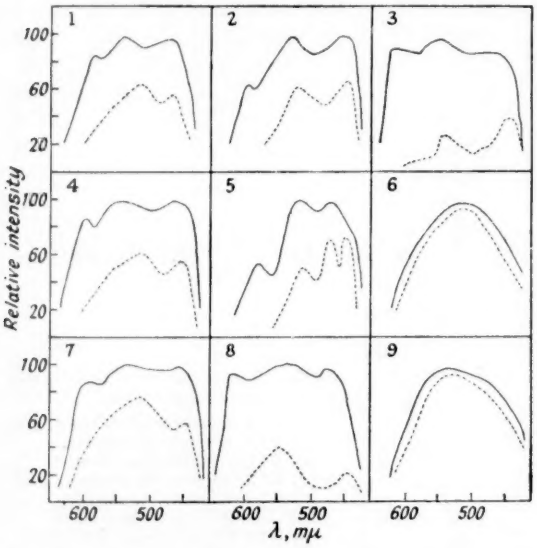


FIG. 5. *Luminescence spectra of colourless (full curves) and coloured (broken curves) modifications.*

(1) 2 : 2′-*Dimethyldianthrone.*
(2) *Xanthylideneanthrone.*
(3) 3 : 4-3′ : 4′-*Dibenzodianthrone.*
(4) 2 : 2′-*Dimethoxydianthrone.*
(5) 4 : 4′-*Dimethyldianthrone.*
(6) *Dixanthylen.*
(7) *Dianthrone.*
(8) 4 : 4′-*Dimethoxydianthrone.*
(9) 4 : 4′-*Dimethoxydixanthylen.*

It is, however, impossible to deduce from the present results whether or not this conversion is complete. (For comparison, the *trans* ⟶ *cis*-photoconversion of azobenzene stops at a photochemical equilibrium of 15—40% of *cis*; Hartley, *J.*, 1938, 633.) The figures

TABLE 1.

Substance	Critical increment (kcal./mole) [a]	log *A* (sec.$^{-1}$) [a]	log $\varepsilon_{max.}$ (photochromism) [b]	log $\varepsilon^{\infty}_{max.}$ (thermochromism) [c]	ΔH, kcal./mole [d]
Group (a):					
4 : 4′-Dimethyldianthrone	16·5	14	3·9	—	—
4 : 4′-Dimethoxydianthrone	11·5	10·5	4·6	—	—
4 : 4′-Dibromodianthrone	15·5	14	4·0	—	—
3 : 4 : 3′ : 4′-Dibenzodianthrone (IV)	20	18	4·0	—	—
Group (b):					
Dianthrone (I)	—	—	4·4	3·7	3·5
2 : 2′-Dimethyldianthrone	16	11·5	4·0	4·0	2·9
2 : 2′-Dibromodianthrone	19	14·5	4·4	4·7	4·1
2 : 2′-Dimethoxydianthrone	16·5	12	4·5	4·0	1·7
3 : 3′-Dibromodianthrone	19	15	4·0	3·7	4·0
Dixanthylen (II)	12·5	13·5	4·2	3·7	5·6
1 : 1′-Dimethoxydixanthylen	12·5	13·5	4·5	4·3	7·2
Xanthylideneanthrone (III)	18·5	16	3·9	4·0	3·5

[a] Accurate within about 2 units. [b] Accurate within about 0·2 unit. [c] It is impossible to assess the error in these values, because of the uncertain extrapolation by which they are obtained (cf. footnote, p. 630). [d] Accurate within about 0·6 unit.

TABLE 2.

Substance	Temp., °K	Conversion % into coloured modification *	Substance	Temp., °K	Conversion % into coloured modification *
Dianthrone (I)	298	0·3	3 : 3′-Dibromodianthrone	298	0·1
	373	1·2		408	0·8
	418	1·6			
			Dixanthylen (II)	363	0·04
2 : 2′-Dimethyldianthrone	298	0·8		408	0·01
	363	2		423	0·13
	418	3			
			4 : 4′-Dimethoxydixanthylen	418	0·04
2 : 2′-Dimethoxydianthrone	298	5		448	0·08
	402	11		458	0·10
	423	13			
			Xanthylidenanthrone (III)	363	1·0
2 : 2′-Dibromodianthrone	298	0·06		408	1·4
	363	0·3			
	418	0·5			

* From $\varepsilon_{max.}/\varepsilon^{\infty}_{max.}$, and therefore subject to the uncertainty mentioned in the footnote on p. 632.

presented in col. 4 of Table 1 may therefore be regarded as minimum values for the ε of the pure coloured modifications.

The near ultra-violet parts of the absorption spectra of the coloured and the colourless forms were practically identical, confirming the results of Grubb and Kistiakowsky (*loc. cit.*) and Theilacker *et al.* (*loc. cit.*) with regard to (I) and (II).

It is evident that photochromism makes possible the investigation of the physical properties of the coloured form at concentrations far exceeding those attainable thermally (cf. Table 2), and it is hoped to obtain the coloured modifications from these solutions in solid form and to study them crystallographically.

The following substances showed neither photochromic nor thermochromic behaviour : Anthrone, 4-bromo-, 4-methyl-, and 4-methoxy-anthrone, xanthen, xanthone, diphenylmethylene- and 4-methoxydiphenylmethylene-anthrone, dithioxanthylen, "*NN*′-dimethyldiacridine," $[C_6H_4\langle^{NMe}_{S}\rangle C_6H_4]_2$.

The total luminescence spectra of the colourless and coloured forms of all the substances showing photochromism were measured in a rigid glassy medium at about −180°. No attempt was made to differentiate between fluorescence and phosphorescence, as defined by Kasha (*Chem. Reviews*, 1947, **41**, 401). No appreciable difference between the two modifications was observed with (II), but with (III) and also with (I) and its derivatives, the luminescence of the coloured modification was weaker and shifted towards shorter wave-lengths (Fig. 5).*

The molar polarisation P of the coloured form was investigated for (III), the other photochromic substances not being soluble enough to allow sufficiently accurate measurements of the increment of the dielectric constant of the solutions. The dielectric constants of toluene η_0 and of a toluene solution of (III) before (η_1) and after (η_2) irradiation were measured at −78°. From the observed increments $\eta_1 - \eta_0 = 0{\cdot}0041$ and $\eta_2 - \eta_0 = 0{\cdot}0110 \pm 0{\cdot}0004$, values of P of 380 ml. for the colourless form and 890 ml. for the coloured form were calculated (for method of calculation, see Fischer, *J. Chem. Physics*, 1951, **15**, 395). The actual value of $P_{coloured}$ is still higher, because under the experimental conditions illumination could not be carried out until there was no further increase in η. The sum of electronic and atomic polarisation being assumed to be equal for the two modifications, it follows from the above results that the orientation polarisation, and therefore the dipole moment, of the coloured form is considerably larger than that of the colourless species. No significant difference was found between the dielectric constants of fresh solutions of the colourless form and of solutions in which colour had been produced by low-temperature

* It was shown by Hirshberg *et al.* (*Bull. Soc. chim.*, 1951, **18**, 88) that anthrone and diphenylmethyleneanthrone and their derivatives mentioned in the preceding paragraph exhibit pronounced phosphorescence, whereas the colourless forms of dianthrone, 4 : 4′-disubstituted dianthrones, and xanthylideneanthrone are practically non-phosphorescent. The "low-temperature thermochromism" described in that communication is probably photochromism produced by stray light.

irradiation and then caused to disappear. It thus seems that for (III) high polarisation, like colour, is a reversible effect of low-temperature irradiation.

Discussion.—(a) *Mechanism of photoconversion.* The existence of a threshold wavelength above which no low-temperature photoconversion occurs suggests that this conversion proceeds in the following steps: (1) absorption of ultra-violet light, raising the molecule to an excited electronic level of the colourless form; (2) transition to an excited electronic level of the coloured form; (3) transfer to the ground level of the coloured form, and "freezing-in" of this form at the low temperatures involved. The critical increments of 12—20 kcal./mole observed show that in the thermal reversion "coloured —→ colourless" potential barriers of at least this height have to be passed (the actual activation energies for the complex molecules involved are probably considerably higher). Such potential barriers indicate that the transformation from one modification into the other involves changes in atomic configuration, a conclusion borne out by the absence of photo-

FIG. 6. *High-temperature attachment to spectrophotometer.*

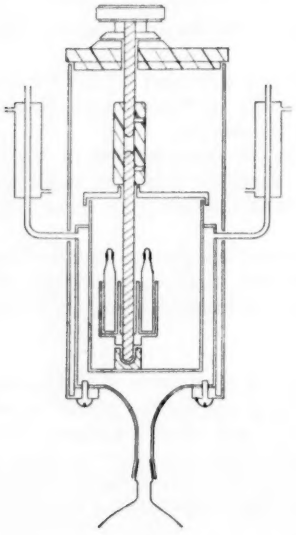
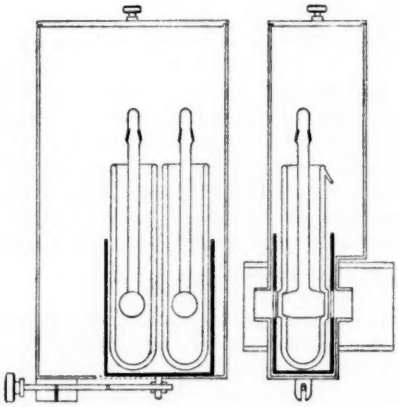


FIG. 7. *Low-temperature attachment to spectrophotometer and Dewar-type cells.*



chromism in the solid state or in rigid media. Photochromism should therefore be exhibited by any substance which, in addition to its normal colourless form, can also exist in a coloured form of the type described above. Thermochromism, on the other hand, represents a thermal equilibrium, the position of which depends on the energy difference between the two modifications. It is, therefore, plausible that for compounds such as those listed in group (*a*) of Table 1, which show only photochromism, this energy difference is so large that no observable shift of the equilibrium towards the coloured species occurs within the accessible temperature range. The absence of photochromism with dithioxanthylen and *NN'*-dimethyldiacridine indicates that, contrary to the view expressed by Theilacker *et al.* (*loc. cit.*), coloured modifications of these substances probably do not exist in solution.

(b) *Nature of the coloured modification.* As pointed out above, the difference between the energy levels of the ground states of the colourless and coloured forms is only a few kcal./mole. However, no conclusion with regard to configurational similarity between the two modifications can be drawn from this fact, because the resonance energies of the two forms may well differ considerably. The high polarity of the coloured modification of (III) shows that dipolar mesomers, such as (III*a*) suggested by Schoenberg *et al.* (*loc. cit.*), contribute materially to the structure of this modification. The transition from one

modification to the other thus appears to involve changes in the electron distribution, as well as in the atomic configuration.

The results described are on the whole not incompatible with Grubb and Kistiakowsky's suggestion (*loc. cit.*) that the coloured modification represents a triplet diradical state.* However, it would be difficult to explain the easy transition between electronic states of dissimilar multiplicity, during irradiation, which one would then have to postulate. Moreover, reactions involving changes in electronic multiplicity should have abnormally low frequency factors, whereas the factors found for the thermal reversion reaction are not smaller than those encountered with common first-order reactions (Laidler, "Chemical Kinetics," McGraw-Hill Book Co. Inc., New York, 1950, p. 108).

In the last analysis only magnetic measurements will make it possible to decide whether or not the coloured modifications described represent an extremely long-lived triplet state of the molecules involved (Kasha, *loc. cit.*). Photochromsism makes such measurements practicable, because of the comparatively high concentrations of the coloured forms attainable.

No final conclusions seem justifiable yet as to the actual nuclear configuration of the two modifications described. However, Grubb and Kistiakowsky's suggestion (*loc. cit.*) about the colourless modification, that " the ground state [of dianthrone] is a singlet, with the double bond in a state of considerable torsion," has recently been shown to be incorrect, at least as far as the solid state is concerned, because the dianthrone molecule is centrosymmetric in the crystal (Harnik, Herbstein, and Schmidt, *Nature*, 1951, **168**, 158). A two-dimensional analysis of the crystal structure of dianthrone has meanwhile led to the suggestion of a centrosymmetric, non-planar model for this molecule (Harnik and Schmidt, forthcoming publication). As to the coloured modification, the fact that it exists also with compounds of group (*a*) in Table 1 suggests that in this modification, too, the two halves of the molecule are not in the same plane. Coplanarity, which would be difficult to attain in compounds of group (*b*), is definitely impossible in compounds of group (*a*), owing to the strong steric interference between the substituents of the 4 : 4'- and 5 : 5'-carbon atoms. (Since the orientation of the two halves of the molecule has not been ascertained, we have numbered all derivatives of dianthrone with the smallest number. Of course, *e.g.*, the 2 : 2'- may really be the 2 : 7'-derivative, and the 4 : 4'- is most probably the 4 : 5'-derivative.)

Experimental

Absorption Spectra.—These were determined by means of a Beckman model D.U. quartz spectrophotometer. Special attachments were made for the measurements at high and at low temperatures. In the high-temperature attachment (Fig. 6) the absorption cells were put into a double-walled container, heated by the vapours of various liquids boiling in an attached Pyrex-glass flask. Silica windows allowed the light to pass through this container. Four silica cells of 1-cm. light path rested in a stand which could revolve in steps of 90°, each step introducing one cell into the light path. The temperature of the solutions could thus be kept constant to within about 5°.

For investigations at low temperatures special Dewar-type cells were designed by Hirshberg and made by the Thermal Syndicate Ltd. for both absorption (Fig. 7) and luminescence (Fig. 8) measurements. For absorption work two cells (containing the solvent and the solution) were placed in the attachment also shown in Fig. 7. The light path in these cells was 2 cm. The external windows of the cells were slightly heated electrically during the measurements in order to keep them clear from fog. The solutions in the cells were kept at the desired low temperature by means of solid carbon dioxide or liquid nitrogen, which were introduced into the Dewar compartment of the cells up to a suitable height.

After photoconversion into the coloured modifications had been effected by irradiation of the cooled cells with a mercury-vapour lamp for the necessary periods (usually 30 seconds were sufficient), the absorption of the solutions was measured.

Luminescence Spectra.—These were photographed with a glass spectrograph on Ilford panchromatic soft gradation plates and evaluated by means of a Leeds and Northrup recording

* Kasha (*loc. cit.*) has already suggested that the transition triplet $\longrightarrow$ excited triplet is responsible for the transient colour formation observed with some compounds during phosphorescence, following strong illumination.

microphotometer. In the arrangement used, the surface of the sample, which was activated by the 365-mμ Hg line from a Hanovia 120-watt type S.100 quartz burner, radiated the luminescent light directly to the slit of the spectrograph, thus reducing losses due to absorption. The angle between exciting and luminescent radiation was about 45° (cf. Hirshberg *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 5117). The solutions were cooled by liquid nitrogen introduced into the Dewar compartment of the cell (Fig. 8). Under these conditions the solvent mixture used (ethanol : toluene : ethyl ether, 1 : 1 : 2 by vol.) formed a rigid, non-luminescent glass. For measurements on the coloured modifications, the latter were produced by irradiation of the cells at about −100° before determination of luminescence.

Rate of Thermal Reversion to Colourless Form.—Capillary m. p. tubes of about 1 mm. internal diameter were filled with the solutions to be investigated (generally in *iso*heptane, m. p. −119°) and sealed under nitrogen. They were then irradiated at the respective low temperatures until maximum colour intensity was reached (under the experimental conditions about one minute sufficed). The capillaries were then quickly transferred to a bath at a low temperature kept constant to ±0·25°. There the capillaries were observed against a white background, and the time needed for the disappearance of colour was recorded. The temperatures were chosen so as to give reversion times of 2—30 minutes, and varied between −5° and −105°, according to the substance investigated.

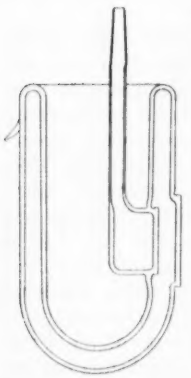


FIG. 8. *Dewar-type cell for measurement of luminescence spectra.*

The limited accuracy aimed at in the present measurements (Table 1) did not warrant the technically difficult introduction of a low-temperature thermostat into the spectrophotometer. The assumption that the colour disappearance is a first-order reaction could therefore not be verified experimentally.

For the calculation of the frequency factor [A in $k = A \exp(-E/\boldsymbol{R}T)$] it was arbitrarily assumed that the " end-point " of the disappearance of colour in the capillaries corresponds to a reversion of 95% of the solute into the colourless form. (Any assumption between 90 and 99·9% reversion would give the same value of log A, within 0·5 unit, whereas an overall error of 2 units for log A has been assumed in Table 1.)

For the determination of the frequency threshold of the photoconversion, the 365, 405, 436, and 546 mμ Hg lines were isolated by suitable filters and used for the irradiation.

Dielectric-constant Increment.—The dielectric constants of the solutions were measured in a slightly modified Sayce–Briscoe cell immersed in a large, unsilvered, silica, Dewar vessel containing alcohol–carbon dioxide snow. The cell could thus be irradiated while in the thermostat. Its contents were mixed during irradiation by applying suction and pressure alternately at one of its two side-tubes.

Materials.—The following substances were prepared according to the references cited: Anthrone (*Org. Synth.*, Coll. Vol. I, New York, 1944, p. 60); xanthone (*ibid.*, p. 552); dianthrone and xanthylideneanthrone (Schoenberg, Ismail, and Asker, *J.*, 1946, 442); dixanthylen (Gurgenjanz and Kostanecki, *Ber.*, 1895, **28**, 2310); xanthen (Heller and Kostanecki, *Ber.*, 1908, **41**, 1324); diphenylmethyleneanthrone (Padova, *Ann. Chim.*, 1910, **19**, 386); *NN'*-dimethyldiacridine (Decker and Peltsch, *J. pr. Chem.*, 1935, **143**, 227). The synthesis of the other substances investigated has been described recently as follows: Anthrone derivatives (4-bromo-, 4-methoxy-, 4-methyl-) and dianthrone derivatives (4 : 4′-dimethyl-, 4 : 4′-dimethoxy-, 4 : 4′-dibromo-, 3 : 3′-dibromo-, 2 : 2′-dimethyl-, 2 : 2′-dimethoxy-, 2 : 2′-dibromo-) by Bergmann and Loewenthal (*Bull. Soc. chim.*, 1952, **19**, 66); 4 : 4′-dimethoxydixanthylen and dithioxanthylen by Bergmann *et al.* (*ibid.*, p. 262); 4-methoxydiphenylmethyleneanthrone by Bergmann *et al.* (*ibid.*, 1951, **18**, 88).

The authors gratefully acknowledge their indebtedness to Dr. E. D. Bergmann for his interest and advice, and for samples of all substances investigated, except those mentioned below, to Mr. E. Loewenthal, B.Sc., for samples of anthrone, dianthrone, and their derivatives, and to Dr. D. Shapiro for a sample of 4 : 4′-dimethoxydixanthylen. They also thank Mr. M. Kaganovitch for technical assistance, and Mr. B. Feldmann and Mr. M. Silbermann for the construction of the attachments to the spectrophotometer.

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129. *The Inhibition of Acetaldehyde Oxidation by Hydrocarbons of Various Molecular Structures.*

By N. J. H. Small and A. R. Ubbelohde.

The method of crossed reaction chains for testing for correspondence between different oxidation mechanisms has been extended. Various hydrocarbons were mixed with the system $CH_3{\cdot}CHO + O_2 + N_2$ (1 : 3·7 : 8·6) undergoing oxidation at 150—250°. The inhibition observed with the *n*-paraffins pentane, hexane, and heptane was found to increase with increasing chain length. In the C_5 series *iso*pentane was a more powerful inhibitor than *n*-pentane, and with pent-2-ene even more pronounced inhibition was observed.

This inhibition is attributed to a non-regenerative crossing with the acetaldehyde oxidation chain

Initiation $CH_3{\cdot}CHO + X \longrightarrow CH_3{\cdot}\dot{C}{=}O + XH$ . . . . . (1)

Chain sequence
$CH_3{\cdot}\dot{C}{=}O + O_2 \longrightarrow CH_3{\cdot}C(O{\cdot}O{-})O$ . . . . . (2)
$CH_3{\cdot}C(O{\cdot}O{-})O + CH_3{\cdot}CHO \longrightarrow CH_3{\cdot}\dot{C}O + CH_3{\cdot}C(O{\cdot}OH)O$ (3)

such that the third step is replaced by

$CH_3{\cdot}C(O{\cdot}O{-})O + RH \longrightarrow CH_3{\cdot}C(O{\cdot}OH)O + R$ . . . . (4)

(where RH is a hydrocarbon molecule)

At the temperatures studied, the R radical appears to be unable to continue a fruitful oxidation chain. Examination of the reaction products suggests that this radical becomes stabilised almost entirely as an olefin. Thus the crossing of the reaction chains at (4) leads to inhibition.

The fact that pent-2-ene is more effective in reaction (4) than the *n*-paraffins accords with the greater ease of abstraction of hydrogen from a methylene group in the α-position to the double bond. The greater inhibitory power of *iso*pentane than of *n*-pentane may likewise be attributed to the lower energy of rupture of the tertiary C–H bond. The correlation of inhibiting power with chain length in *n*-paraffins parallels the ease of oxidation of these molecules at higher temperatures and is tentatively attributed to facilitation of reaction (4) by the increased contribution from vibration coupling in the longer hydrocarbons. Some auto-solvent effects may also result from the increased molecular flexibility of the longer paraffin chains.

The temperature required for uncatalysed oxidation reactions in gaseous paraffins is about 250°, and is so high that the more labile reaction intermediates have only a transient life. They are difficult to detect in the oxidation products and there is therefore considerable speculation concerning the reaction mechanism. For this reason any method of promoting reaction chains at temperatures where the identification of these labile intermediate becomes possible constitutes a major contribution towards the elucidation of controversial points in the slow combustion of paraffin hydrocarbons.

A possible method for inducing oxidation reactions in paraffins involves the method of crossed reaction chains (Small and Ubbelohde, *J.*, 1950, 723). In the previous investigation various hydrocarbons were introduced into an acetaldehyde–air mixture undergoing vigorous oxidation at temperatures below 200°. At these temperatures the hydrocarbons themselves are inert towards molecular oxygen under the conditions of the experiment. The results showed that no oxidation chains for the hydrocarbons investigated could cross

fruitfully with those of acetaldehyde. In some cases, however, the added hydrocarbon had a detectable inhibitory influence in the aldehyde system. This inhibition was interpreted on the basis of hydrogen transfer from the paraffin, which was thought to stabilise aldehyde peroxide radicals so that they could no longer propagate their own reaction chains. Reactions of the type (4) (above) were suggested.

This interpretation implies the liberation of alkyl radicals in the aldehyde system, but at the temperatures used the evidence was against the establishment of a subsequent hydrocarbon oxidation chain such as:

$$R + O_2 \longrightarrow RO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2')$$

$$RO_2 + RH \longrightarrow RO{\cdot}OH + R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3')$$

It has now been verified that inhibition of the aldehyde oxidation by *n*-pentane is accompanied by the production of olefinic material.

An interesting influence of molecular structure on the efficiency of inhibition was suggested by the previous observations. This feature has been further studied. By use of a new reaction vessel and flow rates comparable to those employed previously, it has been established that *n*-pentane, *n*-hexane, and *n*-heptane in equal molecular quantities produce an inhibition on the aldehyde oxidation which increases with chain length in the paraffin. With the other hydrocarbons tested, results indicate a sequence of increasing inhibiting effects in the order *n*-pentane $<$ *iso*pentane $<$ *n*-hexane $<$ *n*-heptane $<$ pent-2-ene.

As is discussed below, structural changes in the hydrocarbon molecule may facilitate the transfer of hydrogen from the hydrocarbon to the aldehyde peroxide radical and thus account for the relative inhibitory efficiencies observed. The greater ease of transfer from an olefin agrees with other knowledge about the ease of disruption of C–H bonds in the α-position to an olefinic bond. The increasing ease of transfer with increasing length of the *n*-paraffin chain parallels certain features of hydrocarbon oxidation.

Experimental

The reaction tube shown in Fig. 1 was similar to that already described by us (in the press), but different methods were used for the collection of reaction products. It was constructed of Pyrex tubing 45 cm. long and had an internal diameter of 3·8 cm. This combustion tube was surrounded by a close-fitting steel furnace heated electrically. Reaction temperatures were recorded axially in the gas flow.

Before entering the combusion chamber the reacting gases were mixed by turbulent flow through closely packed Pyrex chips and glass wool. The reaction mixture consisted essentially of two gas streams whose flow rates were determined by calibrated flow-meters. One of these was nitrogen (approx. 10 c.c./sec.) which passed through a carburettor of acetaldehyde kept in a thermostat at 0° and carried aldehyde molecules into the furnace. The second gas stream was air, which was passed into the reaction tube at a measured rate to supply a source of molecular oxygen for the combustion. When it was desired to study the effects of various paraffins in the aldehyde system, the hydrocarbons were held in separate carburettors kept in thermostats at temperatures such as to give a partial pressure of 280 mm. and were transported to the combustion chamber in the air stream.

The basic reaction taking place in all cases was the oxidation of acetaldehyde, and the aim was to maintain substantially constant conditions for the oxidation except in so far as these became modified by the presence of added diluents.

According to analytical requirements the combustion products were either collected in bubblers (Fig. 1) or were isolated by rapid chilling in collection vessels (Fig. 1*a*) immersed ih carbon dioxide and alcohol. Normally two such traps were used in series.

In view of possible explosion hazards, all combustion reactions took place behind protective screens composed of Perspex and strong steel mesh. When oxidation is extensive, considerable accumulations of organic peroxides can occur and this necessitates the observance of similar precautions in working with undiluted condensates. In practice, thermal explosions were occasionally observed, but these were very mild and only occurred when combustion was in active progress.

Preparation of Materials.—Acetaldehyde. This was obtained by distillation from paraldehyde, a few drops of dilute sulphuric acid being used as depolymerising agent. Gentle warming of the distillation flask on a water-bath prevented excessive charring. The aldehyde was freshly distilled for each run, shielded from strong light, and protected from oxidation by a current of dry, oxygen-free nitrogen.

n-*Pentane.* Because of the special influence of unsaturation it was particularly desirable to remove all traces of unsaturated material from the commercial grades of paraffin hydrocarbons. *n*-Pentane was stored for several weeks over 20% oleum with occasional shaking. The hydrocarbon obtained by decantation was washed with potassium hydroxide and then gently refluxed for 24 hours with a concentrated solution of the same reagent. Repeated washing with water and drying (Na_2SO_4) completed the purification process. This procedure also assisted removal of branched-chain isomers which are more readily sulphonated than *n*-pentane.

Fractional distillation under oxygen-free nitrogen in a 16″ column packed with porcelain rings gave a cut, b. p. 35—36°, n_D^{18} 1·3580, which was used in these experiments.

n-*Hexane.* This was purified in the same way as *n*-pentane. Fractional distillation gave a sample, b. p. 67·5—68·5°, n_D^{18} 1·3810. A carburettor at 41° gave a partial pressure of 280 mm.

n-*Heptane.* This was purified as for *n*-pentane and -hexane. Distillation gave a fraction, b. p. 95·5—97°, n_D^{18} 1·3995. A thermostat at 68° gave a partial pressure of 280 mm.

FIG. 1.

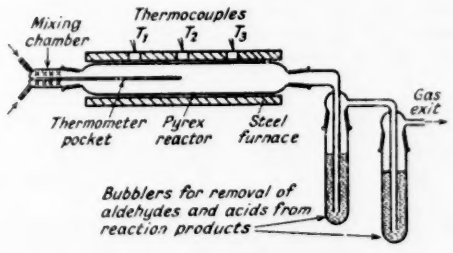
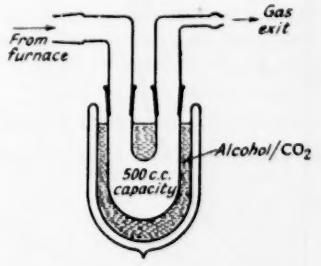


FIG. 1*a*.



Pent-2-ene. This was distilled, b. p. 35—36°/753 mm., n_D^{18} 1·3839, and used without further purification. A carburettor at 6·5° gave p = 280 mm.

iso*Pentane.* Owing to the easier attack of *iso*-hydrocarbons by oleum, a different procedure was used for the separation of any olefins in the sample of commercial *iso*pentane. Blank experiments showed that, whereas olefins of the chain lengths likely to be present were very rapidly brominated when shaken with dilute bromine water, substitution of the bromine into the saturated hydrocarbons was only just perceptible after 24 hours. Light and air were excluded as far as possible, and the commercial *iso*pentane was briefly shaken with bromine water, then immediately washed several times with concentrated sodium hydroxide. The hydrocarbon was distilled through a tube of sodium hydroxide pellets steam-jacketed at 100° to ensure complete removal of hydrogen bromide and organic bromides. The product, collected in a cooled receiver, was fractionated before use, and had b. p. 27°, n_D^{18} 1·3561.

Preparation of Reaction Vessel.—To ensure uniform surface conditions in all experiments, the reaction tube was thoroughly cleaned with equal volumes of concentrated nitric and sulphuric acid at 100° before each run. Abundant washing with water, then distilled water, and drying at 200° completed the cleaning process.

Analysis of Reaction Products.—The general procedure was identical with that described previously (*J.*, 1950, 725). When hydrocarbon had been added to the aldehyde oxidation, the condensate separated into two layers. The hydrocarbon layer was washed with water, and the washings were added to the aqueous layer. The entire aqueous product was then made up to 250 ml. and titrated for peroxide, aldehyde, and acid content by standard procedures. When the bubblers were used, the aqueous scrubbings were made up as a standard solution which could be analysed for reaction products.

Results.—General characteristics of the aldehyde oxidation. The combined yield of peroxide and acid is plotted as a percentage of the aldehyde used in the oxidation in Figs. 2 and 3. Before the addition of hydrocarbon molecules the reaction tube was calibrated with an

acetaldehyde–air mixture corresponding with the reference mixture in the Table below. Fig. 2, curve *A*, plots the general course of oxidation. A smooth curve is obtained showing a steep rise at 190°. Ignition and mild explosion of the reaction mixture occurred at temperatures above 205°. Slow combustion was always accompanied by production of a thin white mist from the exit tube. Curve *B* records the effect of diluting the reference mixture with nitrogen, in proportions similar to those used for the hydrocarbon diluents.

In several of these reference experiments the combustion tube was packed with broken Pyrex chips. Three points (*F*) in Fig. 2 show how the reaction is completely suppressed at temperatures where thermal explosion was observed with the same mixture in an unpacked vessel. At about 250° a reaction then appeared to start and led to the production of a faint mist at the exit tube. An immediate temperature rise to 260°, followed by a further increase to 280°, was probably the result of intense but localised reaction. About 10% of oxidation was obtained, but since the reaction temperature was completely uncontrollable this result is not plotted. This inhibition of oxidation by increasing the extent of surface in the vessel will not be discussed

FIG. 2.

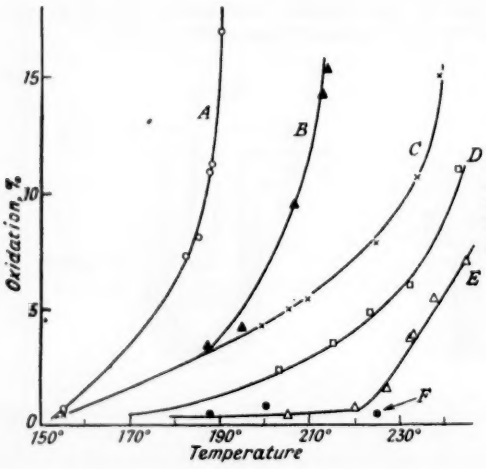
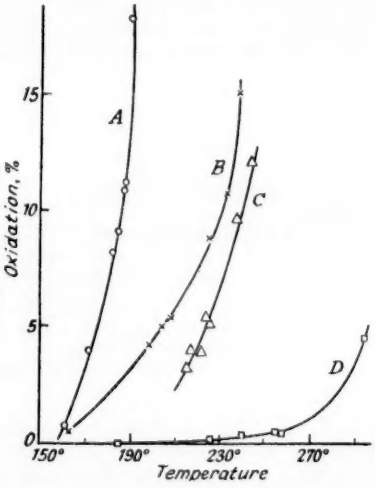


FIG. 3.



in detail here. It seems unlikely that the inhibitions observed on addition of hydrocarbons can be due to wall effects.

Effect of hydrocarbons on the aldehyde oxidation. In this work the aims were to keep essentially constant conditions for the aldehyde oxidation, and to add hydrocarbons in comparable molecular proportions. The extent to which these aims were realised is illustrated in Table 1. It will be observed that for each of the additions the total molar rate of gas flow

TABLE 1. (Flow rates in g.-mols./sec. $\times 10^3$.)

Mixture : CH_3·CHO plus	CH_3·CHO	O_2	N_2	Hydrocarbon	Total flow rate
(Ref. mixture) Figs. 2 and 3, *A*...	0·348	0·0937	0·803	Absent	1·245
N_2, Fig. 2, *B*	0·348	0·0937	0·803	0·276(N_2)	1·512
C_5H_{12}, Fig. 2, *C*; Fig. 3, *B*	0·348	0·0937	0·803	0·284	1·514
C_6H_{14}, Fig. 2, *D*	0·348	0·0937	0·803	0·295	1·517
C_7H_{16}, Fig. 2, *E*	0·348	0·0937	0·803	0·276	1·516
C_5H_{10}, Fig. 3, *D*	0·348	0·0937	0·803	0·255	1·500
iso-C_5H_{12}, Fig, 3, *C*	0·348	0·0937	0·803	0·264	1·509

remained substantially constant during the series. The experimental results plotted in Figs. 2 and 3 show that the percentage of aldehyde oxidised is appreciably reduced in the presence of the paraffin molecules studied.

Under the conditions of these experiments the saturated hydrocarbons do not themselves undergo appreciable oxidation below about 250°. The marked and specific

reduction in overall oxidation when nitrogen is replaced by hydrocarbons, which is observed from as low as 150° upwards, thus cannot be due to attack of the hydrocarbon on molecular oxygen competing with the attack of acetaldehyde on oxygen. It seems likely that the hydrocarbon breaks a proportion of the oxidation chains of the acetaldehyde, by collisions with one of the chain carriers leading effectively to chain termination.

When *n*-paraffins inhibit the oxidation of acetaldehyde it is particularly desirable to determine whether the observed effects are primarily physical, such as the promotion of energy-removing collisions with varying efficiency according to the structure of the hydrocarbon, or whether chemical changes in the hydrocarbon molecule explain the effects observed. To test this point a detailed chemical analysis was carried out on *n*-pentane recovered from the condensing traps. The hydrocarbon material was repeatedly washed with water until the last washings gave negative reactions with Schiff's reagent. Normally only a few washings were required before all water-soluble aldehydes were removed. After being dried (Na_2SO_4) the hydrocarbon was divided into two samples. One sample was carefully fractionated; no evidence could be obtained for the formation of long-chain aldehydes such as valeraldehyde in the residues of fractionation. The other sample was tested for olefins, a sensitive method of analysis being necessary. Blank experiments were made on synthetic mixtures of pent-2-ene and *n*-pentane. The general procedure was to add excess of standard solution of bromine in carbon tetrachloride to a mixture, and store it in the dark in a stoppered vessel. The extent of bromine absorption was determined volumetrically at various time intervals. It was verified that the bromine reacted very rapidly in the presence of any unsaturated material but only very slowly (by substitution) with the *n*-hydrocarbon.

When this procedure was used with recovered pentane, the sample showed a slight but definite bromine absorption, indicating that some of the *n*-pentane used had been converted into olefinic material. Typical results are recorded in Table 2. Measurements of refractive

TABLE 2. *Bromine values of hydrocarbon solutions.*

Hydrocarbon	n_D^{18}	Time of contact with Br_2, hr.	Bromine absorbed, %
Pure *n*-pentane	1·3580	1	0
		4½	0
		50	0·104
n-Pentane + ⅛% of amylene (Synthetic mixture)	1·3590	½	0·428
		1	0·412
		26	0·437
Recovered hydrocarbon (washed and dried)	1·3590	½	0·246
		4½	0·247
		16½	0·294

indices were also carried out on the same hydrocarbon samples. The figures given above confirm the formation of olefins in the recovered material, but refractive indices are insufficiently sensitive for definite measurements in view of the small amounts of unsaturation involved.

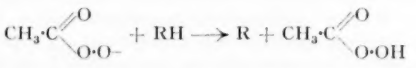
DISCUSSION

The main result from the present study of crossed reaction chains in the oxidation of acetaldehyde is to confirm that a number of molecules which might be expected to propagate oxidation actually act as inhibitors. One striking illustration from the figures is that this inhibition changes what would be a thermal explosion around 200° to a slow combustion.

The influence of molecular structure on inhibiting efficiency is noteworthy. The range of molecules so far studied gives a suggestive though not a complete picture. When the information available is combined with other results on the oxidation mechanism and on the influence of structure on hydrocarbon reactivity, certain problems can be focused more sharply.

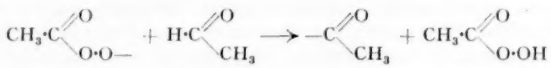
(i) The production of olefins from paraffins, accompanying the inhibition process, suggests that this is closely associated with transfer of hydrogen from the hydrocarbon molecules to a chain carrier in the oxidation of acetaldehyde. This hypothesis was suggested in our earlier publication (*J.*, 1950, 723) and has been adopted recently by Farmer and McDowell (*Trans. Faraday Soc.*, 1952, **48**, 624) to explain the inhibitory

effect of alcohols in the oxidation of acetaldehyde. The fact that pentene is much more efficient than the *n*-paraffins as an inhibitor supports this suggestion, since the C–H bond proximate to C=C is known to be more readily disrupted than in a paraffin (Farmer, *ibid.*, 1942, **38**, 348). The greater inhibition by *iso*pentane than of *n*-pentane also appears to be due to the lower energy of disruption of the tertiary C–H bond in *iso*pentane. On the basis of the reaction scheme outlined above, the chemical aspect of the inhibition can be formulated as :

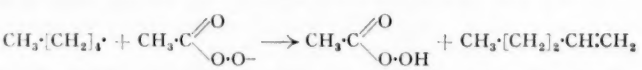


. . . . . (4)

competing with



At the temperatures used, the R radicals in (4) are unable to propagate the chain efficiently, so that partial inhibition of the oxidation of the acetaldehyde results. The subsequent fate of these R radicals is to produce olefins, possibly by disproportionation : $2R \longrightarrow RH + R'{\cdot}CH{:}CH_2$, or by other chain-terminating reactions such as



The yields of olefins so far obtained are definite but too small to permit detailed chemical analysis.

(ii) The marked efficiency of hydrogen as an inhibitor (Small and Ubbelohde, *Nature*, 1951, **168**, 201 ; and results in the press) and the increasing efficiency of paraffin inhibition as the chain lengthens suggest that energy removal in collisions with an activated chain carrier may also be important in the inhibition. As discussed elsewhere (Ubbelohde, *Proc. Roy. Soc.*, 1935, *A*, **152**, 354; Small and Ubbelohde, *locc. cit.*) for the case of hydrocarbon oxidation, the processes in the oxidation chain

$$RH + X \longrightarrow XH + R \quad \text{or} \quad RO_2 + RH \longrightarrow RO{\cdot}OH + R$$

are thermoneutral or endothermic, whereas (2) (above) and $R + O_2 \longrightarrow RO_2^*$ are exothermic. Further reaction of the energy-rich RO_2^* will occur most easily before this exothermic energy is dissipated by collisions. It seems likely that hydrogen is particularly efficient in deactivating RO_2^*. The increased range of coupled vibrations in the *n*-paraffins with increasing chain length might be playing a similar rôle in facilitating energy transfer in deactivating collisions such as $RO_2^* + RH \longrightarrow RO_2 + (RH)^*$. Collisions of this type could also be favoured by the crumpling of the *n*-paraffins (cf. Ubbelohde, *Rev. Inst. franç. Pétrole*, 1949, **4**, No. 9, 488) which in the limit makes the energy transfer similar to that in a solvent (the " auto-solvent effect "). These aspects of the reactivity of hydrocarbons are under further investigation.

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130. *The Synthesis of Thyroxine and Related Substances. Part XI.* Diphenylamines.*

By R. C. Cookson.

In the presence of dimethylaniline *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester reacted with toluene-*p*-sulphonyl chloride followed by *p*-anisidine to give the dinitrodiarylamine (V; R = Me, R′ = H). Reduction of the last, tetrazotisation of the diamine, and treatment with tri-iodide solution produced the iodobenzotriazole (XI). The same series of operations with the derived *N*-acetyl derivative (V; R = Me, R′ = Ac) gave the related iodobenziminazole (XIII; R = Me, R′ = Et, R″ = Ac).

4′-Hydroxy-4-methyl-3 : 5-dinitrodiphenylamine underwent reversible oxidation to the quinone imine (VI), which added hydrogen chloride to form exclusively the 3′-chloro-4′-hydroxydiphenylamine (VII). With *n*-butylamine, however, the imine gave equimolecular quantities of the butylaminoquinone imine (X) and original hydroxydiphenylamine.

A series of *N*-benzoyl-2 : 6-di-iodo-diphenylamines (XV) was made by rearrangement of the imidates (XIV), easily got by condensation of the 2 : 6-di-iodophenols with *N*-*p*-methoxyphenylbenzimidoyl chloride. Preferential hydrolysis of the *N*-benzoyl group in (XV) was achieved by potassium hydroxide and of the *O*-methyl group by hydriodic acid.

THE only known analogue of thyroxine in which the central oxygen atom has been replaced is the sulphide prepared by Harington (*Biochem. J.*, 1948, **43**, 434), which had 1/5th the activity of thyroxine in the tadpole metamorphosis test and presumably no significant anti-thyroxine activity. Experiments on the synthesis of the " diphenylamine analogue," in which this oxygen atom is replaced by a secondary amino-group, have now been carried out.

A possible route to the necessary 2 : 6-di-iododiphenylamines seemed to be indicated by the synthesis of 2 : 6-di-iododiphenyl ethers from 2 : 6-dinitrophenols recently developed in these laboratories. In this the dinitrophenol is converted by toluene-*p*-sulphonyl chloride in pyridine into the 1-(2 : 6-dinitrophenyl)pyridinium toluene-*p*-sulphonate (I); this condenses with a phenol to give the 2 : 6-dinitrodiphenyl ether (Parts II, III, and V, *J.*, 1949, S 190, S 199, 3424) which can then be reduced to the diamine. This can be tetrazotised in sulphuric–acetic acids, and the diazonium groups replaced by iodine (Parts I and V, *J.*, 1949, S 185, 3424).

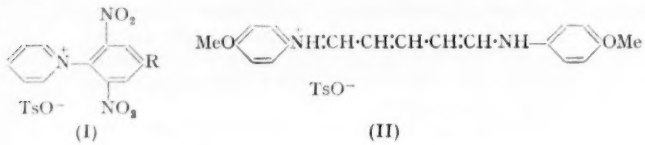
The pyridinium salt (I; R = Me) obtained from 3 : 5-dinitro-*p*-cresol (Me = 1) reacted vigorously with *p*-anisidine, to give 3 : 5-dinitro-*p*-toluidine and purple crystals of 5-*p*-anisidinopentadienal *p*-methoxyanil toluene-*p*-sulphonate (II); the latter, when heated, cyclised, with loss of *p*-anisidine, to 1-*p*-methoxyphenylpyridinium toluene-*p*-sulphonate, identified by comparison of the corresponding picrate with an authentic sample. This reaction is a variant of Zincke's method for opening the pyridine ring, in which 1-(2 : 4-dinitrophenyl)pyridinium halides react with primary aromatic amines to give 2 : 4-dinitroaniline and the hydrohalides of glutacondialdehyde " dianils " (Zincke *et al.*, *Annalen*, 1904, **330**, 361; **333**, 296; 1905, **338**, 107). Incidentally, it provides a much milder and more convenient method for converting dinitrophenyl toluene-*p*-sulphonates into dinitroanilines than the action of dry ammonia on the esters in boiling nitrobenzene or xylene (Ullmann and Nádai, *Ber.*, 1908, **41**, 1873; Ullmann and Sané, *ibid.*, 1911, **44**, 3730). The pyridinium toluene-*p*-sulphonate made from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester, for example, yielded (III) on treatment with *p*-anisidine.

In the absence of pyridine bases 2 : 4- and 2 : 6-dinitrophenyl toluene-*p*-sulphonates react with aromatic amines to form the dinitrodiphenylamines. The procedure may be simplified by allowing the amine to react with the ester (which may be the toluene-*p*-sulphonate or chloride, depending on the phenol) prepared *in situ* by treating the dinitro-

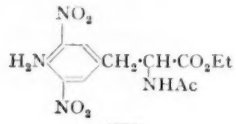
* Part X, *J.*, 1952, 2366.

phenol with toluene-*p*-sulphonyl chloride in diethylaniline (Ullmann *et al.*, *loc. cit.*; Sané and Joshi, *J. Indian Chem. Soc.*, 1932, **9**, 59; Joshi, *ibid.*, 1933, **10**, 677).

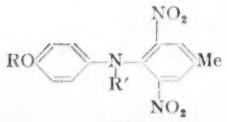
p-Anisidine reacted with 3 : 5-dinitro-*p*-cresol that had been treated with toluene-*p*-sulphonyl chloride in dimethylaniline, and the diphenylamine (IV; R = Me, R′ = H) was isolated from the dark red mixture. The yield of pure diphenylamine was disappointingly low compared with those reported by Ullmann *et al.* (*loc. cit.*) for the dinitrodiphenylamines made similarly from aniline and the toluidines (40% against 90—98%). The ester (V; R = Me, R′ = H) was prepared in the same way from *N*-acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester in a yield of only 25%. This was raised to 59% by using chloroform as solvent instead of dimethylaniline, which was reduced to 2 mols. No strictly comparable experiments were done on the effect of diluents on the yield, but chloroform or dioxan were used in all later experiments.



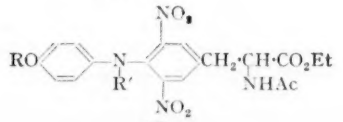
(I) (II)



(III)



(IV)



(V)

(TsO = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}O$)

The 4′-hydroxydiphenylamines (IV; R = R′ = H) and (V; R = R′ = H) were prepared by essentially the same method from *p*-aminophenol. The possibility that the hydroxy- as well as the amino-group might react unless the dinitrophenyl ester was always presented with an excess of *p*-aminophenol, together with the sparing solubility of *p*-aminophenol in most organic solvents, made a slight modification in technique necessary; the dinitrophenol was caused to react with toluene-*p*-sulphonyl chloride as before, and the resulting solution was added slowly to an excess of *p*-aminophenol in boiling dioxan. In this way (IV; R = R′ = H) was obtained as dark red needles, but (V; R = R′ = H) was a gum, which was characterised as the crystalline *O*-acetate (V; R = Ac, R′ = H). In all these experiments the dinitrodiphenylamine was accompanied by a dark red oil, the original dinitrophenol, and (even in the absence of excess of toluene-*p*-sulphonyl chloride) the toluene-*p*-sulphonyl derivative of the amine.

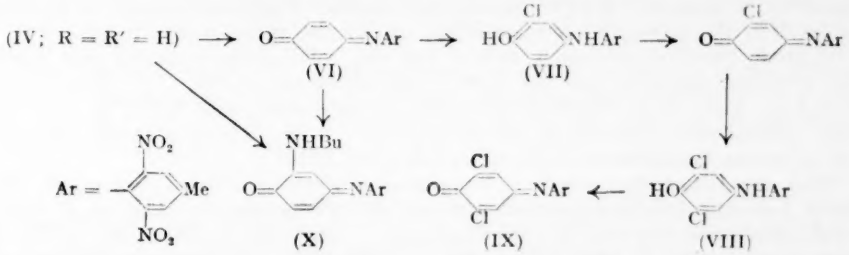
With acetic anhydride in pyridine the hydroxydiphenylamines rapidly gave the *O*-acetates, but much more drastic conditions were needed for formation of the *N*-acetates, namely, use of sulphuric or perchloric acid as catalyst in a large excess of acetic anhydride; toluene-*p*-sulphonic acid and sodium acetate were ineffective as catalysts. Unfortunately, the more important *N*-acetates (V; R = Me, R′ = Ac; R = R′ = Ac) were uncrystallisable. The *N*-benzoates could not be prepared by normal methods, such as long boiling of the amines with benzoyl chloride and pyridine in xylene. The *N*-acetate (IV; R = H, R′ = Ac) could be prepared indirectly from (IV; R = R′ = H) by hydrolysis of the *ON*-diacetate (IV; R = R′ = Ac) with one equivalent of methanolic alkali.

In an attempt at iodination, 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (IV; R = R′ = H) and iodine monochloride in acetic acid gave the monochloro-derivative (VII) but no iodo-compound. Small proportions of chloro-compounds may be expected from the action of iodine monochloride on phenols, but such an extreme example appeared unique. However, the *N*-acetyl derivative (IV; R = H, R′ = Ac) with iodine in aqueous ethylamine gave a product analyses of which agreed fairly well for the di-iodo-compound.

The *p*-hydroxydiphenylamine (IV; R = R′ = H) was dehydrogenated by oxidising agents to *p*-benzoquinone 4-methyl-2 : 6-dinitroanil (as VI), which could be hydrolysed to *p*-benzoquinone and 3 : 5-dinitro-*p*-toluidine. Hydrosulphite (dithionite) or hydriodic acid reduced the quinone anil back to the hydroxydiphenylamine, although the latter

was oxidised by iodine in the presence of base (which removes hydrogen iodide from the equilibrium mixture).

Addition of hydrogen chloride to the quinone anil (VI) led to the chloro-compound produced by the action of iodine monochloride on the hydroxydiphenylamine (IV : R = R′ = H). The mechanism of the latter reaction thus becomes clear : there is first oxidation by iodine monochloride to (VI), most of which then adds hydrogen chloride to form (VII) while part is reduced back to (IV; R = R′ = H) by the resulting hydrogen iodide, with formation of iodine. These were indeed the products isolated. Successive dehydrogenation and addition of hydrogen chloride were applied to the synthesis of the 3 : 5-dichloro-4-hydroxy-compound (VIII), which could be further dehydrogenated to (IX). That the addition of hydrogen chloride to the quinones had occurred in the direction stated was confirmed by the production of the same diphenylamine (VIII) by condensation of 4-chloro-3 : 5-dinitrotoluene with 4-amino-2 : 6-dichlorophenol in the presence of sodium acetate.

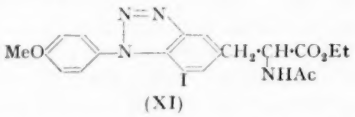


Orton (*J.*, 1908, **314**; 1927, **2854**) found that 2 : 6-dichlorobenzoquinone and 2 : 3 : 6-trichlorobenzoquinone 2′ : 4′ : 6′-trichloro-anils with hydrogen chloride formed respectively 2 : 3 : 6 : 2′ : 4′ : 6′-hexachloro- and 2 : 3 : 5 : 6 : 2′ : 4′ : 6′-heptachloro-4-hydroxydiphenylamine, and interpreted this reaction as partial reduction of the quinone anil by hydrogen chloride to the hydroxydiphenylamine, which was then chlorinated by the free chlorine produced, so that the reaction would eventually go to completion. However, in view of the probable reduction potentials of the quinone anils, the amount of free chlorine at equilibrium would be infinitesimal; direct 1 : 4-addition of hydrogen chloride to the quinone is much more likely. This explains why only one product is formed, and why the ethers of the hydroxydiphenylamines produced by reduction of the quinone anils are not chlorinated.

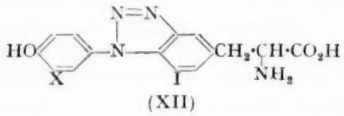
With *n*-butylamine, (VI) gave equimolecular quantities of (IV; R = R′ = H) and the butylaminoquinone anil (X). Addition of butylamine must initially give the butylamino-hydroxydiphenylamine. But the butylamino-group (unlike the chloro-group) is electron-releasing, and its substitution into a quinone lowers the reduction potential (Fieser and Fieser, *J. Amer. Chem. Soc.*, 1935, **57**, 491), so that the butylaminohydroxydiphenylamine is immediately oxidised to the butylaminoquinone anil (X) by unchanged quinone anil (VI), itself reduced to the hydroxydiphenylamine (IV; R = R′ = H). Provided that addition of butylamine is slow compared with establishment of the oxidation–reduction equilibrium, the products should be (X) and (IV; R = R′ = H), in agreement with experiment. Although (IV; R = R′ = H) did not react appreciably with iodine in organic solvents, in the presence of *n*-butylamine a vigorous reaction took place with production of the butylaminoquinone anil (X). Oxidation of the hydroxydiphenylamine by iodine proceeds in the presence of the amine, which adds on as before, but with the oxidising agent reaction can go to completion to give (X) and butylamine hydriodide. The structure (X), rather than that of the 2′-butylamino-isomer, is assigned to the product on theoretical grounds and by analogy with the products from addition of hydrogen chloride. The compound was dark purple and formed neither salts nor an acetyl derivative, owing to the conjugation of the butylamino- with the nitro-groups.

The dinitrodiphenylamine (V; R = Me, R′ = H) is less easily reduced than the comparable dinitrodiphenyl ethers, presumably owing to greater conjugation of the *o*-nitro-

groups with nitrogen than with oxygen. In the presence of palladium–charcoal at 110°/70 atm., but not at room temperature, reduction yielded the gummy diamine. The Sandmeyer reaction (Parts I and V), then gave the expected benzotriazole (XI) (cf. Saunders, "The Aromatic Diazo-Compounds," 2nd Edn., Arnold, 1944, pp. 247, 263), hydrolysed by hydriodic–acetic acid to the amino-acid (XII; X = H). Although several methods were tried, only one more atom of iodine could be introduced into this phenol, leading to (XII; X = I).



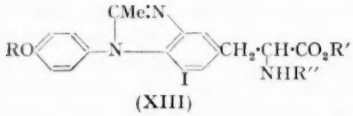
(XI)



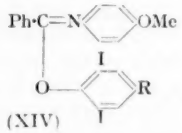
(XII)

In order to protect the imino-group (V; R = Me, R′ = H) was acetylated and then reduced to the diamine. Both compounds were gums. Under the influence of the strong acid used in the attempted tetrazotisation one of the amino-groups reacted with the acetyl group before diazotisation, so that the only solid product isolated after reaction with tri-iodide solution was the 2-methylbenziminazole (XIII; R = Me, R′ = Et, R″ = Ac). This could be hydrolysed to the hydroxy-amino-acid (XIII; R = R′ = R″ = H). Attachment of $R{\cdot}SO_2^-$ to the nitrogen atom of the diphenylamine should prevent such cylisation, but attempts to introduce this group failed.

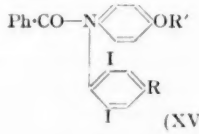
After the failure to convert 2 : 6-dinitrodiphenylamines into 2 : 6-di-iododiphenylamines, I investigated the isomerisation of aryl *N*-arylbenzimidates (XIV) to *N*-benzoyl-2 : 6-di-iododiphenylamines (XV) (cf. Chapman, *J.*, 1925, 1992; 1927, 1743; 1929, 569; Jamison and Turner, *J.*, 1937, 1954; Hall, *J.*, 1948, 1603). No iodo-compound has been subjected to this reaction, but electron-attracting groups in the migrating nucleus, and electron-releasing groups in the other nucleus, are known to facilitate it. Rearrangement of an ester such as (XIV) might well take place at a lower temperature than pyrolytic loss of iodine.



(XIII)



(XIV)



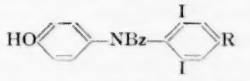
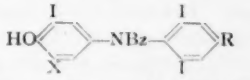
(XV)

The esters (XIV) were prepared in the conventional way, by condensing the imidoyl chloride with the sodium salt of the di-iodophenol in an anhydrous solvent or, more conveniently, with the free di-iodophenol in pyridine. The ester (XIV; R = Me) was selected as a model for a trial of the rearrangement, because of its electronic similarity with [XIV; R = $CH_2{\cdot}CH(NHAc){\cdot}CO_2Et$]. In the first attempts, at 190° to 250° without a solvent, the products were gums. Three hours' boiling in nitrobenzene (b. p. 209°) gave the rearranged compound (XV; R = R′ = Me) in 50% yield. After various trials (see Experimental section) it was found that ten minutes' boiling in diphenyl ether (b. p. 259°) or diphenyl (254°) and extraction with light petroleum afforded the amide in about 55% yield without chromatography. Hydriodic acid in acetic acid demethylated (XV; R = R′ = Me), leaving the hindered amide group intact—a fortunate selectivity in view of the ability of iodine in alkaline solution, involved in the next stage, to dehydrogenate *p*-hydroxydiphenylamines to quinone anils. Treatment of (XVI; R = Me) with iodine in ethylamine then led to the tetraiodo-compound (XVII; R = Me, X = I) in high yield.

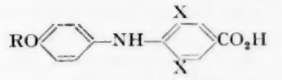
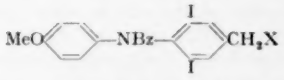
However, the *N*-*p*-methoxyphenylbenzimidic esters from *N*-acetyl-3 : 5-di-iodo-DL- or -L-tyrosine ethyl ester were gums, as also were the products obtained by their isomerisation. 3 : 5-Di-iodo-DL-tyrosine hydantoin and the imidoyl chloride gave a gel, from which only unchanged hydantoin and benz-*p*-anisidide could be isolated.

After the failure of this direct synthesis the work was concentrated on preparing amides (XV) in which R could later be elaborated into the alanine side chain. In agreement with the effect of electron-attracting groups in this position, the ester (XIV; R = CO_2Me)

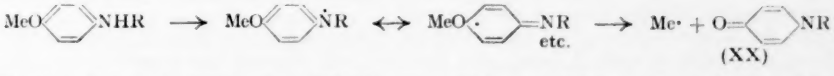
changed into (XV; R = CO_2Me, R′ = Me) almost quantitatively on 1·5 hours' boiling in *o*-dichlorobenzene (b. p. 179°). Hydriodic acid in acetic acid then gave the hydroxy-acid (XVI; R = CO_2H), but the action of 2 mols. of iodine in potassium carbonate solution led only to the tri-iodo-compound (XVII; R = CO_2H, X = H).

(XVI)   (XVII)

The *N*-benzoyl-4′-methoxydiphenylamine ester (XV; R = CO_2Me, R′ = Me) was hydrolysed by dilute alkali to the acid (XV; R = CO_2H, R′ = Me), from which the benzoyl group was removed by 40% potassium hydroxide, yielding (XVIII; R = Me, X = I). The corresponding 4′-hydroxy-compound (XV; R = CO_2H, R′ = H), however, was recovered unchanged from boiling 40% potassium hydroxide, perhaps owing to the negative charge conferred on the second benzene ring by the phenoxide ion. On the other hand, although the 4′-methoxy-amide (XV; R = CO_2Me, R′ = Me) was smoothly demethylated to the 4′-hydroxy-amide (XV; R = CO_2H, R′ = H) by hydriodic acid, the 4′-methoxy-amine (XVIII; R = Me, X = I), in which the electron pair of the nitrogen atom is no longer prevented by the benzoyl group from spreading to the 2 and the 6 position of the benzene ring, underwent reduction as well as demethylation to give 4′-hydroxydiphenylamine-4-carboxylic acid (XVIII; R = X = H).

(XVIII)   (XIX)

This investigation was ended before alternative methods of demethylating 2 : 6-di-iodo-4′-methoxydiphenylamines had been explored, but one method that might be applicable to the iodo-compounds was used to demethylate the 4′-methoxy-2 : 6-dinitrodiphenylamine (V; R = Me, R′ = H), at the same time leaving the acetyl and the ester group in the side chain intact. It utilised the susceptibility of the *p*-aminophenyl ether system to oxidation. *N*-Bromosuccinimide in dioxan oxidised (V; R = Me, R′ = H) to the quinone anil (XX), which on reduction and acetylation yielded (V; R = Ac, R′ = H), identical with the sample described previously. This reaction, may involve diphenylimine radicals:



Heating the ester (XV; R = CO_2Me, R′ = Me) with lithium aluminium hydride in ether or dioxan was without effect or caused loss of iodine. The bromide (XIX; X = Br) resulted from the action of *N*-bromosuccinimide in the presence of benzoyl peroxide on (XV; R = R′ = Me), but the yield was low and erratic. Only gums could be isolated after the aldehyde (XIV; R = CHO), which should rearrange relatively easily, had been heated.

Experimental

*N-Acetyl-4-amino-3 : 5-dinitro-*DL*-phenylalanine Ethyl Ester.*—*N*-Acetyl-3 : 5-dinitro-DL-tyrosine ethyl ester (3 g.) and toluene-*p*-sulphonyl chloride (1·8 g., 1·1 mols.) in pyridine (15 c.c.) were heated at 110° for ½ hour. *p*-Anisidine (4·3 g., 4 mols.) in pyridine (4·3 g.) was added to the cooled solution, which immediately became deep purplish-red, changing to reddish-brown on heating. After 1 hour at 110° the mixture was cooled and poured into chloroform, which was washed with water and then 2N-hydrochloric acid, dried (Na_2SO_4–Na_2CO_3), and distilled. The dark reddish-brown residue of the p-*amino*-compound crystallised when scratched. Recrystallised from alcohol, it (1·9 g., 63%) had m. p. 152—153°. Another crystallisation from benzene in the presence of charcoal yielded the pure compound as golden-yellow blades, m. p. 153—154° (Found: C, 46·1; H, 5·0. $C_{13}H_{16}O_7N_4$ requires C, 45·9; H, 4·7%).

This amine (0·3 g.), pyridine (0·65 c.c., 1·2 mols.), benzoyl chloride (0·85 c.c., 1·1 mols.), and toluene (1·5 c.c.) were boiled for ¾ hours. The cooled mixture was filtered from pyridine

hydrochloride, which was washed with more toluene. The toluene solution was washed with water, dried, and concentrated. The yellow crystals of the p-*benzamido*-compound which separated on cooling were filtered off and washed (yield, 0·19 g.). Recrystallisation from toluene gave yellow needles, m. p. 175—176° (Found : C, 53·8; H, 4·4. $C_{20}H_{20}O_8N_4$ requires C, 54·1; H, 4·5%).

Reaction between 1-(4-*Methyl*-2 : 6-*dinitrophenyl*)*pyridinium Toluene*-p-*sulphonate and* p-*Anisidine*.—3 : 5-Dinitro-*p*-cresol (10 g.), toluene-*p*-sulphonyl chloride (10 g., 1 mol.), and pyridine (30 c.c.) were hreated at 110° for ½ hour and then cooled. Addition of *p*-anisidine (18 g., 3 mols.) in pyridine (9 c.c.) caused immediate development of a deep purple-red colour and evolution of heat. After 1 hour the mixture, containing a mass of dark purplish-blue crystals, was poured into water. The solid was filtered off, and thoroughly extracted with acetone, leaving 5-p-*anisidinopentadienal* p-*methoxyanil toluene*-p-*sulphonate* (20·8 g., 86%). It separated from methanol in metallic, purple-blue crystals, m. p. 149° (Found : C, 64·7; H, 6·0; N, 5·7. $C_{26}H_{28}O_5N_2S$ requires C, 65·1; H, 5·8; N, 5·8%). Concentration of the acetone solution gave orange-yellow needles of 3 : 5-dinitro-*p*-toluidine (8·0 g., 80%), m. p. 171° after recrystallisation from alcohol.

When the salt of the dianil (3·0 g.) was boiled in chlorobenzene (14 c.c.) for about 1·5 minutes the colour began to fade rapidly and an oil to separate. After 10 minutes the mixture was cooled, and the oil, which had crystallised, was filtered off (2·0 g., 90%). 1-p-*Methoxyphenyl*-*pyridinium toluene*-p-*sulphonate* separated from ethyl alcohol–acetate in colourless plates, m. p. 180° (Found : C, 64·0; H, 5·5. $C_{19}H_{19}O_4NS$ requires C, 63·9; H, 5·3%). This reaction proceeded also in boiling *n*-butanol, pyridine, or nitrobenzene. Addition of aqueous sodium picrate to a solution of the salt in water precipitated the pyridinium picrate as pale yellow needles, m. p. 162—164°, unchanged by admixture of the picrate with an authentic sample.

4′-*Methoxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—3 : 5-Dinitro-*p*-cresol (10 g.) was heated with toluene-*p*-sulphonyl chloride (10 g., 1 mol.) in dimethylaniline (30 c.c.) at 110° for ½ hour. *p*-Anisidine (18 g., 3 mols.) in dimethylaniline (9 c.c.) was added to the cooled mixture, which immediately became dark red with the separation of much solid and evolution of heat. After 1 hour the pasty mass was dissolved in chloroform, which was washed with 2N-hydrochloric acid, and water, dried, and distilled. The residue set to a sticky mass on scratching, but recrystallisation from various solvents did not yield a clean product. Chromatography in benzene on alumina led to the pure *diphenylamine*, deep red plates [from light petroleum (b. p. 100—120°)], m. p. 132—134° (6 g., 39%) (Found : C, 55·45; H, 4·3; N, 13·8. $C_{14}H_{13}O_5N_3$ requires C, 55·45; H, 4·3; N, 13·9%). The broad, brick-red, very strongly adsorbed band at the top of the chromatogram was extruded and boiled with water, yielding red needles of the sodium salt of 3 : 5-dinitro-*p*-cresol, evidently formed from the phenol by reaction with sodium ions on the highly alkaline grade of alumina used.

When the diphenylamine (1 g.) was boiled for 1 hour in acetic anhydride (5 c.c.) containing sulphuric or perchloric acid (1 drop), and the resulting mixture was poured into water the N-*acetyl* derivative was precipitated (1·05 g., 92%). After recrystallisation from alcohol–benzene and then alcohol the yellow needles melted at 189° (Found : N, 12·2. $C_{16}H_{15}O_6N_3$ requires N, 12·3%).

N-*Acetyl*-4-p-*anisidino*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester*.—*N*-Acetyl-3 : 5-dinitro-DL-phenylalanine ethyl ester (30 g.), toluene-*p*-sulphonyl chloride (18 g., 1·1 mols.), and dimethylaniline (25 c.c., 2·2 mols.) in chloroform (100 c.c.) were boiled for 1 hour. *p*-Anisidine (16 g., 1·5 mols.) in chloroform (25 c.c.) was added. A dark red colour very rapidly developed and colourless, water-soluble crystals separated (probably a salt of dimethylaniline). After an hour's boiling the chloroform solution was washed with N-hydrochloric acid, dried (Na_2SO_4), and distilled. The viscous oil which remained was dissolved in alcohol and very carefully diluted with water. The red needles of the *diphenylamine* (23·0 g., 59%) melted at 142—145°. Later crops were contaminated with toluene-*p*-sulphon-*p*′-anisidide, m. p. 114° after purification. Further recrystallisation of the diphenylamine raised the m. p. to 146° (Found : C, 53·9; H, 4·8; N, 12·8. $C_{20}H_{22}O_6N_4$ requires C, 53·8; H, 4·9; N, 12·6%).

When dimethylaniline was used as solvent and the second stage of the reaction was allowed to proceed at room temperature (with spontaneous heating), the yield of diphenylamine after chromatography was only 25%.

Acetylation of the diphenylamine in hot acetic anhydride containing sulphuric or perchloric acid produced a yellow oil, uncrystallisable even after chromatography.

4′-*Hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—3 : 5-Dinitro-*p*-cresol (10 g., 0·96 mol.), toluene-*p*-sulphonyl chloride (10 g., 1 mol.), dimethylaniline (13·3 c.c., 2 mols.), and dioxan

(35 c.c.) were boiled for ½ hour. This solution was dropped, during 10 minutes, into a vigorously boiling solution of *p*-aminophenol (11 g., 1·9 mols.) in dioxan (60 c.c.). A colourless solid separated from the red solution. After another 20 minutes' boiling the mixture was poured into dilute hydrochloric acid. The precipitate was washed with water and recrystallised from alcohol, yielding dark red needles (9·9 g., 68%), m. p. 160—168°. Repeated recrystallisation gave a sample of ***amine*** melting at 174—175° (Found: C, 52·0; H, 3·9; N, 13·3. $C_{13}H_{11}O_5N_3,\frac{1}{2}H_2O$ requires C, 52·3; H, 4·1; N, 14·1%).

Acetic anhydride (0·072 c.c., 1·1 mols.) was added to the amine (0·2 g.) in pyridine. The dark red colour faded to orange. After 1 hour the solution was diluted with water and the orange needles of the O-***acetate*** were filtered off (0·23 g., 100%). They separated from alcohol or benzene–*cyclo*hexane as compact, bright red crystals, m. p. 157° (Found: C, 54·6; H, 4·0. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%).

Acetic anhydride (2 c.c. per 0·3 g. of amine) containing a trace of sulphuric acid on the steam-bath for a few minutes led to the *diacetate* (0·32 g., 83%), pale yellow needles (from acetone–alcohol), m. p. 186° (Found: C, 54·65; H, 4·0; N, 11·15. $C_{17}H_{15}O_7N_3$ requires C, 54·7; H, 4·0; N, 11·3%). Half the above amount of acetic anhydride led to, mainly, the *O*-acetate, which with more acetic anhydride–sulphuric acid gave the diacetate.

The diacetate (0·15 g.) was suspended in warm methanol (1 c.c.) and acetone was added until it dissolved (*ca.* 2 c.c.). Methanolic potassium hydroxide (1·07 c.c.; 21 g./l.; 1 mol.) was added, causing an immediate darkening in colour of the solution. After 2 hours at 45°, the solution was poured into water. Addition of acetic acid (2 drops) to the clear brownish-orange solution precipitated crystals of the ***amide*** (0·12 g., 90%), m. p. 192—193°. Recrystallisation from alcohol–*cyclo*hexane gave yellow needles, m. p. 245° (Found: C, 54·3; H, 4·0. $C_{15}H_{13}O_6N_3$ requires C, 54·4; H, 3·9%). Repetition of this preparation yielded the high-melting form at once.

N-*Acetyl*-4′-*hydroxy*-3′ : 5′-*di*-*iodo*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—To the above *N*-acetyldiphenylamine (250 mg.) in 33% aqueous ethylamine (4 c.c.), iodine in aqueous potassium iodide solution (1·6 c.c.; 244 g./l.; 2 mols.) was slowly added with shaking. After 2 hours the pale yellowish-brown crystals that had separated were filtered off, washed with water, and dried (230 mg.). They could not be recrystallised and were, therefore, dissolved in aqueous alcohol and decomposed by dilute hydrochloric acid. On scratching, the yellow emulsion formed deposited the solid *iodo*-compound (120 mg.). After two recrystallisations from alcohol the yellow crystals melted at 140—144° to a brown liquid (Found: C, 31·6; H, 2·15; N, 6·5; I, 41·6. $C_{15}H_{11}O_6N_3I_2$ requires C, 30·9; H, 1·9; N, 7·2; I, 43·5%).

4-(p-*Acetoxyanilino*)-N-*acetyl*-3 : 5-*dinitro*-DL-*phenylalanine Ethyl Ester*.—*N*-Acetyl-3 : 5-dinitro-DL-phenylalanine ethyl ester (13·9 g.), toluene-*p*-sulphonyl chloride (8·0 g., 1·05 mols.), and dimethylaniline (10·3 c.c., 2 mols.) were boiled in dioxan (60 c.c.) for ½ hour. This solution was dropped during 20 minutes into *p*-aminophenol (14 g.) in boiling dioxan (80 c.c.). After a further ½ hour's boiling the mixture was poured into dilute acid, which was extracted with chloroform. Evaporation of the chloroform left a dark red syrup (23 g.). A previous experiment had shown that this did not crystallise after chromatography on alumina and reprecipitation from various solvents, but that the *O*-acetate was crystalline. The product was, therefore, dissolved in pyridine (100 c.c.), to which acetic anhydride (7·5 c.c.) was added. After ½ hour the solution was diluted with chloroform, washed with dilute hydrochloric acid, and evaporated. The oily residue was dissolved in alcohol. Addition of water until cloudiness appeared caused the separation of only oil. Excess of water was therefore added and the whole extracted with chloroform. The dried extract was passed down a 2-ft. column of activated alumina. The red oil resulting from the evaporation of the first eluate was dissolved in hot alcohol. Orange-yellow needles of the ***acetoxy-amine*** (4·6 g.) separated on cooling. A second crop (4·8 g.) was obtained by dilution of the mother-liquors with water. After two recrystallisations from alcohol the needles melted at 184° (Found: C, 52·6; H, 4·2; N, 11·85. $C_{21}H_{22}O_9N_4$ requires C, 53·2; H, 4·6; N, 11·8%).

The fraction immediately following the diphenylamine (still with chloroform as eluant) separated from alcohol, after treatment with charcoal, as plates (0·5 g.), m. p. 141°, undepressed by *p*-toluene-*p*′-sulphonamidophenyl acetate prepared by treatment of *p*-aminophenol in pyridine with toluene-*p*-sulphonyl chloride followed by acetic anhydride and recrystallisation from toluene.

The eluate obtained by using chloroform–methanol (2 : 1) left a dark red syrup of unacetylated hydroxydiphenylamine on evaporation. This was dissolved in pyridine and treated with more acetic anhydride (10 c.c.). Dilution with water after ½ hour produced needles of the acetoxy-compound (2·0 g.) (total yield, 59%).

Treatment of the acetoxydiphenylamine with a large excess of acetic anhydride containing perchloric acid gave a yellow gum, which did not crystallise.

p-*Benzoquinone* 4-*Methyl*-2 : 6-*dinitroanil*.—Addition of a solution of *N*-bromosuccinimide (0·31 g., 2 mols.) in dioxan (10 c.c.) to the dark red solution of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (0·25 g.) in dioxan (10 c.c.) caused the colour to fade to orange-yellow in a few minutes. After ¼ hour the mixture was poured into water and the pale yellow precipitate, m. p. 185—187°, was filtered off. Recrystallisation from alcohol gave golden-yellow needles of the *quinone anil* (0·23 g., 90%), m. p. 193° (Found: C, 54·4; H, 3·2; N, 14·6. $C_{13}H_9O_5N_3$ requires C, 54·4; H, 3·1; N, 14·6%). The reaction could also be carried out in boiling carbon tetrachloride, but this was less convenient because of the low solubility of the diphenylamine.

Other agents used successfully for the oxidation were chromic acid in acetic acid, alcoholic ferric chloride, iodine in dioxan containing tri-*n*-propylamine, and mercuric oxide.

For preparative purposes the most convenient oxidant was mercuric oxide; a benzene solution of the diphenylamine was boiled with a slight excess of mercuric oxide for 10 minutes after the colour indicated that dehydrogenation was complete. After filtration from mercury and unchanged oxide and concentration of the solution, *cyclo*hexane was added to the boiling solution until crystals appeared. On cooling, needles of the pure anil separated in almost quantitative yield.

Reduction. Sodium dithionite solution (1 c.c.; 66 g./l.; 1 mol.) was added dropwise to a well-shaken solution of the anil (110 mg.) in dioxan (3 c.c.). Dilution with water precipitated red needles of 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine (100 mg., 90%), m. p. and mixed m. p. 169—172°. Hydriodic acid or *p*-aminophenol also effected the reduction.

Hydrolysis. When the anil was boiled with sulphuric acid the pungent smell of benzoquinone could be detected. The anil (100 mg.) was boiled for 1 hour in a mixture of 2N-sulphuric acid (3 c.c.) and dioxan (2 c.c.). The orange blades of 3 : 5-dinitro-*p*-toluidine which separated on cooling (65 mg., 95%) had m. p. and mixed m. p. 170—171°.

3′-*Chloro*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—(a) *From* 4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*. The diphenylamine (1 g.) in acetic acid (10 c.c.) was treated with 15% iodine monochloride in acetic acid (7·5 c.c., 2 mols.). Having been heated on the steam-bath for 1 hour the mixture was poured into sodium hydrogen sulphite solution and extracted with ethyl acetate, which was then washed with sodium hydrogen carbonate solution. The residue after evaporation of the solvent recrystallised from alcohol. The red plates (0·7 g.) began to sinter at 156° and melted at 182—188°. Three recrystallisations from alcohol raised the m. p. of the *chlorodiphenylamine* to 193—195° (Found: C, 48·3; H, 3·0; N, 13·2. $C_{13}H_{10}O_5N_3Cl$ requires C, 48·25; H, 3·1; N, 13·0%). A small amount of unchanged 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine was isolated by fractional crystallisation of the material remaining in the first two mother-liquors.

Acetylation (acetic anhydride–pyridine) gave an almost quantitative yield of the *acetate*, bright orange needles, m. p. 182—184° (from alcohol) (Found: N, 11·7. $C_{15}H_{12}O_6N_3Cl$ requires N, 11·5%).

(b) *From* p-*benzoquinone* 4-*methyl*-2 : 6-*dinitroanil*. A solution of the anil (1·5 g.) in dioxan (25 c.c.) was saturated with dry hydrogen chloride. After ½ hour the solution was poured into water, precipitating a red oil, which crystallised when scratched (1·7 g., 100%). After one recrystallisation from alcohol the m. p. was 193—195°, unchanged by the specimen described above. The product obtained by adding concentrated hydrochloric acid to a solution of the anil in acetic acid was less pure.

3-*Chloro*-p-*benzoquinone* 4′-*Methyl*-2′ : 6′-*dinitroanil*.—A solution of the chlorodiphenylamine (1·5 g.) in benzene (25 c.c.) was boiled with mercuric oxide (1·5 g., 1·5 mols.) for ½ hour, filtered, and evaporated. The residue was recrystallised from acetone–alcohol (charcoal). The orange-yellow needles of the *chloroquinone-anil* melted at 198° (1·4 g., 94%) (Found: N, 12·8; Cl, 10·8. $C_{13}H_8O_5N_3Cl$ requires N, 13·1; Cl, 11·0%).

3′ : 5′-*Dichloro*-4′-*hydroxy*-4-*methyl*-2 : 6-*dinitrodiphenylamine*.—Dioxan saturated with hydrogen chloride (5 c.c.) was added to a solution of the monochloroquinone anil (0·7 g.) in dioxan (10 c.c.). The oil obtained by diluting the solution with water crystallised later (yield 0·75 g., 96%). The *dichlorodiphenylamine* crystallised from benzene in red needles, m. p. 240—241° (Found: C, 43·5; H, 2·5; Cl, 19·6. $C_{13}H_9O_5N_3Cl_2$ requires C, 43·6; H, 2·5; Cl, 19·8%).

3 : 5-*Dichloro*-p-*benzoquinone* 4′-*Methyl*-2′ : 6′-*dinitroanil*.—The dichlorodiphenylamine (0·25 g.) was boiled with mercuric oxide (0·25 g., 1·7 mols.) in benzene (15 c.c.) for 1 hour. On cooling, orange crystals of the *quinone-anil* (0·16 g., 64%) separated. A second crop, obtained

by concentration of the mother-liquor, was contaminated by some unchanged diphenylamine. The first crop crystallised from benzene–*cyclo*hexane in orange-yellow fibres, m. p. 208° (Found: C, 43·5; H, 2·25; Cl, 20·3. $C_{13}H_7O_5N_3Cl_2$ requires C, 43·8; H, 2·0; Cl, 19·95%).

Direct Chlorination of 4′-Hydroxy-4-methyl-2 : 6-dinitrodiphenylamine.—Chlorine was passed into a solution of the diphenylamine (0·5 g.) in acetic acid (15 c.c.) for 8 minutes. After about ½ minute the colour had faded to yellow. 20 Minutes later the solution was poured into water. The precipitate was filtered off, washed, and recrystallised from alcohol (*ca.* 100 c.c.). Rather brownish orange-yellow needles (0·36 g.) formed, more being obtainable by dilution of the mother-liquor with water (0·16 g.). Two more crystallisations from alcohol gave the *trichloro*-compound, m. p. 208—212° (Found: C, 40·0; H, 1·5; Cl, 25·75. $C_{13}H_6O_5N_3Cl_3$ requires C, 40·0; H, 1·5; Cl, 27·2%).

The only compound isolated after 1 hour's boiling with dioxan–2N-sulphuric acid (1 : 1) was unchanged chloro-compound.

*3-Butylamino-*p*-benzoquinone 4′-Methyl-2′ : 6′-dinitroanil.*—(a) *From 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine.* Iodine (1·55 g., 4 g.-atoms) in pyridine (10 c.c.) was added with shaking to a solution of the diphenylamine (0·88 g.) in pyridine (5 c.c.) and *n*-butylamine (3 c.c.). The mixture became hot, and very dark, greenish-brown. After a few minutes the mixture was gradually diluted with water (*ca.* 200 c.c.), and the purplish-black precipitate produced was filtered off (1·05 g.). Recrystallisation twice from alcohol and once from *cyclo*hexane containing a little benzene gave purple needles of the *butylaminoquinone anil*, m. p. 184° (Found: C, 57·0; H, 5·8; N, 15·6. $C_{17}H_{18}O_5N_4$ requires C, 57·0; H, 5·0; N, 15·6%).

A small-scale experiment indicated that dioxan as solvent instead of pyridine gave a purer product.

A similar reaction took place when piperidine or morpholine was substituted for butylamine, but the products failed to crystallise.

(b) *From* p*-benzoquinone 4-methyl-2 : 6-dinitroanil. n*-Butylamine (1·5 c.c.) in dioxan (5 c.c.) was added to a solution of the anil (1·0 g.) in dioxan (20 c.c.). The mixture rapidly became deep red. After ½ hour it was cautiously diluted with water, and thus separated into two fractions. The first crop (0·48 g.) began to sinter at 173° and melted at 183—185°. After recrystallisation from *cyclo*hexane containing a little benzene, the purple needles (0·35 g.) melted at 186—187°, unchanged when mixed with the previous sample of butylaminoquinone anil. The second crop (0·62 g.) crystallised from alcohol as red needles (0·3 g.), m. p., alone and mixed with 4′-hydroxy-4-methyl-2 : 6-dinitrodiphenylamine, 169—171°.

*N-Acetyl-4-(4-ketocyclohexa-2 : 5-dienylideneamino)-3 : 5-dinitrophenyl-*DL*-alanine Ethyl Ester.*—A freshly made solution of *N*-bromosuccinimide (0·8 g., 2 mols.) in dioxan (15 c.c.) was added to one of *N*-acetyl-4-*p*-anisidino-3 : 5-dinitrophenyl-DL-alanine ethyl ester (1·0 g.) in dioxan (20 c.c.). After having been kept for 1·5 hours at *ca.* 45° the mixture was diluted with water. The resulting yellow emulsion gradually deposited the *quinone imine* (0·7 g.), m. p. 184° after two recrystallisations from alcohol (Found: C, 52·9; H, 4·3; N, 13·1. $C_{19}H_{18}O_8N_4$ requires C, 53·0; H, 4·2; N, 13·0%).

1-p-*Methoxyphenyl-6′-iodobenzotriazole-4′-*(*N-acetyl-*DL*-alanine Ethyl Ester*) (XI).—*N*-Acetyl-4-*p*-anisidino-3 : 5-dinitro-DL-phenylalanine ethyl ester (5·0 g.) in dioxan (100 c.c.) was hydrogenated in the presence of palladium–charcoal (6%, 1·0 g.) at 110°/75 atm. for 2 hours. The catalyst and solvent were removed in an atmosphere of carbon dioxide, leaving the diamine as an almost colourless gum. This was slowly added in acetic acid (15 c.c.) to sulphuric acid (8 c.c.) at <15°. The resulting solution was added during ¾ hour to a stirred solution of sodium nitrite (1·6 g., 2·1 mols.) in sulphuric acid (30 c.c.) and acetic acid (50 c.c.) kept below −2°. After the very dark solution had stood at 0° for 1 hour it was allowed to run into a solution of sodium iodide (18 g.), iodine (15 g.), and urea (2 g.) in water (300 c.c.) and chloroform (100 c.c.) at 35—40°. After ½ hour the lowest, black, tarry layer was separated, dissolved in alcohol, treated with sodium hydrogen sulphite, and poured into water. The black tar was extracted with ethyl acetate, which was then washed with water, dried ($MgSO_4$), and evaporated. The residual syrup was later induced to crystallise (4·9 g.). The chloroform extract from the reaction mixture after removal of iodine and evaporation yielded a gum from which more solid material (0·5 g.) separated on scratching under warm alcohol (total crude yield, 95%). Two recrystallisations from alcohol and one from toluene gave colourless crystals of the *benzotriazole*, m. p. 152—154° (2·9 g., 51%) (Found: C, 47·1; H, 4·1; N, 10·7. $C_{20}H_{21}O_4N_4I$ requires C, 47·2; H, 4·1; N, 11·0%).

1′-*p-Hydroxyphenyl-7′-iodobenzotriazole-5′-alanine.*—The preceding compound (1·6 g.) was boiled in acetic acid (8 c.c.) and hydriodic acid (5 c.c.) for 1 hour. The cooled solution was

diluted with water and neutralised with dilute ammonia solution. The precipitated *amino-acid* crystallised from hot water in colourless blades (1·1 g., 82%) (Found : C, 40·5; H, 3·75; N, 12·6. $C_{15}H_{13}O_3N_4I,H_2O$ requires C, 40·7; H, 3·4; N, 12·7%).

1′-(*4-Hydroxy-3-iodophenyl*)-7′-*iodobenzotriazole-5′-alanine* (XII; X = I).—The preceding amino-acid (55 mg.) in 33% ethylamine (1 c.c.) was treated with iodine (4·2 g.-atoms) in aqueous potassium iodide (0·27 c.c., 244 g./l.). After 1 hour the solution was diluted to 5 c.c. and made neutral with dilute acetic acid. The flocculent, pale brown precipitate was washed, and dissolved in a large volume of boiling water. The colloidal solution formed on cooling had deposited the *di-iodo*-compound, m. p. 210—214° (decomp.), as a fine, colourless powder by next morning (Found : I, 46·4. $C_{15}H_{12}O_3N_4I_2$ requires I, 46·2%).

Iodine monochloride (2 mols.) in acetic acid also produced the di-iodo-compound.

7′-*Iodo*-1-p-*methoxyphenyl*-2-*methylbenziminazole-5′*-(*N-acetyl*-DL-*alanine Ethyl Ester*) (XIII; R = Me, R′ = Et, R″ = Ac).—The product from the acetylation of *N*-acetyl-4-*p*-anisidino-3 : 5-dinitro-DL-phenylalanine ethyl ester (12 g.) with hot acetic anhydride and perchloric acid was purified by chromatography in chloroform on alumina. The resulting yellow gum was hydrogenated in alcohol containing palladium–charcoal at 70°/60 atm. After removal of the catalyst and solvent under carbon dioxide the diamine remained as an almost colourless glass (11·3 g.).

A solution of the diamine (11·3 g.) in acetic acid (30 c.c.) was added to sulphuric acid (15 c.c.) at 0°. The mixture was then dropped into a solution of sodium nitrite (42 g., 2·3 mols.) in sulphuric (30 c.c.) and acetic (50 c.c.) acids at <0°, during 1 hour. After another ½ hour at 0° the mixture was run into a solution of sodium iodide (25 g.), iodine (18 g.), and urea (3 g.) in water (380 c.c.) at 35°. An hour later the dark tarry lower layer, containing some free iodine, was separated and dissolved in 85% alcohol. Free iodine was eliminated by addition of sodium hydrogen sulphite. Dilution with a large volume of water produced a cloudy solution which was neutralised with sodium carbonate and extracted repeatedly with ethyl acetate. After being washed with water and dried (Na_2SO_4), the extract was evaporated to a syrup which was dissolved in alcohol. Cautious dilution with water then caused separation of the *benziminazole* (2·5 g., 19% from the dinitrophenylamine). Further dilution precipitated a little gum from which no solid could be separated. The product was recrystallised from aqueous alcohol (charcoal). Careful attention to the concentration and temperature was necessary to avoid its deposition as an oil. Two more crystallisations from benzene yielded colourless needles, m. p. 189—191° (1·6 g.) (Found : N, 7·9; I, 24·8. $C_{22}H_{24}O_4N_3I$ requires N, 8·1; I, 24·4%).

1′-*p-Hydroxyphenyl*-7′-*iodo*-2-*methylbenziminazole*-4′-DL-*alanine*.—The foregoing ester (250 mg.) in acetic acid–hydriodic acid (2 : 1, 3 c.c.) was boiled for 1·5 hours. Slow neutralisation of the diluted liquid with ammonia precipitated the *amino-acid* as an amorphous solid (140 mg., 67%). After long boiling in water it crystallised, but then could not be redissolved even in a large volume. It was, therefore, reprecipitated from hot dilute ammonia solution by dilute acetic acid. Great care was necessary to avoid its separation as an emulsion or gum; it had m. p. 234—236° (decomp.) (Found : I, 29·0. $C_{17}H_{16}O_3N_3I$ requires I, 29·1%).

Iodophenyl Imidates.—2 : 6-*Di-iodo*-4-*methylphenyl* N-p-*methoxyphenylbenzimidate*. Benzanisidide (25 g.) and phosphorus pentachloride (23 g., 1 mol.) were heated on the steam-bath till no more hydrogen chloride was evolved. After the phosphoryl chloride produced had been removed at the water pump, the imidoyl chloride crystallised on cooling. A solution of this in dioxan (75 c.c.) was added to one of di-iodocresol (61 g., 1·2 mols.) in alcohol (150 c.c.) containing sodium (2·8 g., 1·1 g.-atoms). Sodium chloride was immediately precipitated and the *ester* soon crystallised. It was washed with alcohol and water (yield, 47 g., 75%). Recrystallisation from alcohol–dioxan gave colourless crystals, m. p. 158—160° (Found : I, 44·7. $C_{21}H_{17}O_2NI_2$ requires I, 44·6%).

4-*Carbomethoxy*-2 : 6-*di-iodophenyl* N-p-*methoxyphenylbenzimidate*. Sodium (0·28 g., 1 g.-atom) in methanol (10 c.c.) was added to methyl 4-hydroxy-3 : 5-di-iodobenzoate (4·9 g., 1·1 mols.) in dioxan (20 c.c.), immediately followed by a solution of the imidoyl chloride from benzanisidide (2·5 g.) in dioxan (10 c.c.). After 1 hour the mixture was poured into water and the oil which crystallised on being scratched was recrystallised from carbon tetrachloride. The colourless rhombohedra of *ester* (4·0 g.) melted at 184°. Light petroleum (b. p. 100—120°) was added to the mother-liquors, and most of the carbon tetrachloride was distilled off. The solvent was decanted from the heavy crystals of ester (0·8 g., total yield, 71%), before the needles of unchanged ester separated (Found : C, 43·3; H, 2·9; I, 41·2. $C_{22}H_{17}O_4NI_2$ requires C, 43·1; H, 2·8; I, 41·4%).

4-*Formyl*-2 : 6-*di-iodophenyl* N-p-*methoxyphenylbenzimidate*. A solution of this *ester* in alcohol–dioxan made as above from benzanisidide (2·5 g., 1 mol.) and 4-hydroxy-3 : 5-di-iodo-

benzaldehyde (5·0 g., 1·2 mols.) was poured into water. The syrup was extracted with benzene, evaporation of which gave an oil that later solidified. After crystallisation from carbon tetrachloride–light petroleum and then *cyclo*hexane the blades melted at 134° (Found: C, 43·0; H, 2·9; I, 43·9. $C_{21}H_{15}O_3NI_2$ requires C, 43·25; H, 2·6; I, 43·5%).

Condensation in pyridine. To get a clean product by this method it seemed important to use imidoyl chloride free from phosphoryl chloride. Since the recrystallisation of such a low-melting solid was difficult and wasteful it was purified by removing as much phosphoryl chloride as possible at the pump, adding benzene, concentrating the mixture, adding light petroleum (b. p. 40—60°), and removing the solvent again from the filtered solution.

4-*Carbo*-n-*butoxy*-2 : 6-*di-iodophenyl* N-p-*methoxyphenylbenzimidate.* The imidoyl chloride (1·2 g., 1·1 mols.) and *n*-butyl 4-hydroxy-3 : 5-di-iodobenzoate (2·0 g., 1 mol.) were dissolved in pyridine (10 c.c.). 3 Hours later the solution was poured into water and the brown oil extracted with ethyl acetate, which was washed with dilute hydrochloric acid and then water. Evaporation left a gum that crystallised. The *ester* separated from methyl cyanide as large rhombohedra (2·7 g., 92%), m. p. 170—172° (Found: I, 38·9. $C_{25}H_{23}O_4NI_2$ requires I, 38·7%).

2 : 4 : 6-*Tri-iodophenyl* N-p-*methoxyphenylbenzimidate.* This *compound*, made by the same method, formed colourless plates (65%) (from acetone–alcohol), m. p. 135—136° (Found: I, 56·1. $C_{20}H_{14}O_2NI_3$ requires I, 55·9%).

The 4 : 6-*di-iodo*-2-*methylphenyl ester* crystallised from ethyl acetate–alcohol in colourless needles (90%), m. p. 145—146° (Found: I, 44·2. $C_{21}H_{17}O_2NI_2$ requires I, 44·6%).

Rearrangements.—N-*Benzoyl*-2 : 6-*di-iodo*-4′-*methoxy*-4-*methyldiphenylamine—In nitrobenzene.* 2 : 6-Di-iodo-4-methylphenyl *N*-*p*-methoxyphenylbenzimidate (4·0 g.) in nitrobenzene (6 c.c.) was boiled under reflux for 3 hours. A little free iodine and the nitrobenzene were removed at 160° (bath) at the water-pump. The residue was extracted from some tar with benzene (110 c.c.) and chromatographed on alumina. The first fractions, crystallised from alcohol, gave the pale brown *amide* (2·0 g., 50%). A colourless sample for analysis, got by crystallisation from light petroleum (b. p. 100—120°) (charcoal), had m. p. 191° (Found: C, 43·7; H, 3·6; I, 43·9. $C_{21}H_{17}O_2NI_2$ requires C, 44·3; H, 3·0; I, 44·6%).

In diphenyl ether. The ester (4·0 g.) in diphenyl ether (10·0 g.) was boiled for 10 minutes. The solution became very dark and iodine vapour appeared. The cooled mixture was extracted twice with boiling light petroleum (b. p. 100—120°) leaving a dark tar. On cooling, the petroleum deposited crystals (2·25 g., 56%) of the rearranged compound. It was best finally purified by crystallisation from 90% acetic acid with charcoal.

Effect of solvent. Samples of the ester (2·0 g.) were boiled in various solvents (5 c.c.) and the amide produced was extracted from the product with light petroleum (b. p. 100—120°). The table shows the yields (%) of rearranged compound.

		Time of boiling (min.)					
Solvent	B. p.	1	5	10	15	30	90
Ph_2O	259°	30	45	55	—	43	—
Ph_2	254	—	—	53	—	—	—
Ph_2O–$PhNO_2$ (4 : 1)	240	—	—	—	45	—	—
o-$C_6H_4Me{\cdot}NO_2$	224	—	—	—	—	34	—
$PhNO_2$	209	—	—	—	—	30	—
o-$C_6H_4Cl_2$	180	—	—	—	—	—	0

Methyl N-*Benzoyl*-2 : 6-*di-iodo*-4′-*methoxydiphenylamine*-4-*carboxylate.*—A solution of 4-carbomethoxy-2 : 6-di-iodophenyl *N*-*p*-methoxyphenylbenzimidate (4·0 g.) in *o*-dichlorobenzene (12 c.c.) was boiled for 80 minutes. Light petroleum (b. p. 100—120°) was then added until crystals began to separate from the boiling solution. On cooling, the *amide* (3·8 g., 95%) was filtered off; it had m. p. 205° [from toluene–light petroleum (b. p. 100—120°)] (Found: C, 42·9; H, 2·7; I, 40·8. $C_{22}H_{17}O_4NI_2$ requires C, 43·1; H, 2·8; I, 41·4%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6-*di-iodo*-4-*methyldiphenylamine.*—The 4′-methoxy-compound (3·1 g.) in acetic acid (15 c.c.) and hydriodic acid (10 c.c.) was boiled for ½ hour. The solid 4′-*hydroxy*-compound was filtered from the cooled solution and recrystallised from acetic acid–dioxan as colourless crystals (2·8 g., 93%), decomp. from 296°, m. p. 306—307° (Found: C, 43·2; H, 2·9; I, 45·8. $C_{20}H_{15}O_2NI_2$ requires C, 43·2; H, 2·7; I, 45·8%).

N-*Benzoyl*-4′-*hydroxy*-2 : 6 : 3′ : 5′-*tetraiodo*-4-*methyldiphenylamine.*—The preceding phenol (1·8 g.) in dioxan (40 c.c.) and ethylamine (30 c.c.; 40%) was treated dropwise with iodine (4 g.-atoms) in potassium iodide solution (6·9 c.c.; 245 g. I_2/l.). After 3 hours the solution was neutralised with dilute acetic acid. The precipitated *tetraiodide* crystallised from alcohol–

dioxan in colourless needles (2·3 g., 88%), m. p. 260—275° (decomp.) (Found: I, 62·6. $C_{20}H_{12}O_2NI_4$ requires I, 62·9%).

N-Benzoyl-4-bromomethyl-2 : 6-di-iodo-4'-methoxydiphenylamine.—The 4-methyl compound (1·63 g.) and *N*-bromosuccinimide (0·56 g., 1·1 mols.) in carbon tetrachloride (25 c.c.) containing a trace of benzoyl peroxide were boiled for an hour. A little more peroxide was then added and the boiling continued for 4 hours. The hot solution was filtered and then mixed with *cyclo*hexane. The solid was filtered off and recrystallised from benzene containing some *cyclo*hexane. The succinimide (m. p. 122—124°) that first separated were removed and the solution then deposited small crystals (0·9 g.), m. p. 187—197° After another crystallisation from benzene–*cyclo*hexane there still appeared to be some succinimide, so the solid was washed with water and crystallised again. The needles of the *bromide* melted at 198—201° (Found: C, 38·7; H, 2·5. $C_{21}H_{16}O_2NBrI_2$ requires C, 38·9; H, 2·5%).

N-Benzoyl-4'-hydroxy-2 : 6-di-iododiphenylamine-4-carboxylic Acid.—The 4'-methoxy-4-methyl ester (3·0 g.) in acetic acid (15 c.c.) and hydriodic acid (10 c.c.) was boiled for 1·5 hours. The colourless crystals of *hydroxy-acid* which formed when the solution was diluted with water were recrystallised from aqueous acetic acid, and then had m. p. 278—280° after sintering from 270° (2·3 g., 80%) (Found: C, 41·3; H, 2·5; I, 43·4. $C_{20}H_{13}O_4NI_2$ requires C, 41·05; H, 2·2; I, 43·4%).

N-Benzoyl-4'-hydroxy-2 : 6 : 3'-tri-iododiphenylamine-4-carboxylic Acid.—Potassium carbonate solution was added to a suspension of the preceding hydroxy-acid (0·5 g.) in hot water (5 c.c.) until a clear solution was obtained. This solution was kept at *ca.* 60° while iodine solution (1·85 c.c., 245 g./l.; 4·2 atoms) was added slowly, potassium carbonate being added occasionally to keep the solution clear and alkaline. After a trace of metabisulphite had been added the solution was acidified. Recrystallisation of the precipitate from acetic acid containing a little water gave the colourless *tri-iodo-acid*, which began to lose iodine at 264°, sintered at 270°, and decomposed at 292° (Found: C, 33·7; H, 2·0; I, 53·2. $C_{20}H_{12}O_4NI_3$ requires C, 33·8; H, 1·7; I, 53·6%).

N-Benzoyl-2 : 6-di-iodo-4'-methoxydiphenylamine-4-carboxylic Acid.—A solution of methyl *N*-benzoyl-2 : 6-di-iodo-4'-methoxydiphenylamine-4-carboxylate (4·39 g.) in alcohol (40 c.c.) and 10N-sodium hydroxide (5 c.c.) was refluxed for 1 hour. Acidification of the solution with hydrochloric acid precipitated a sticky solid. This was washed with alcohol and crystallised from aqueous acetic acid to yield a solid (3·07 g.), m. p. 145—150° (frothing), probably a hydrate. A sample crystallised from toluene yielded the colourless *acid*, m. p. 230° (Found: N, 2·35; I, 41·9. $C_{21}H_{15}O_4NI_2$ requires N, 2·35; I, 42·4%).

2 : 6-Di-iodo-4'-methoxydiphenylamine-4-carboxylic Acid.—A solution of the above acid (1 g.) and potassium hydroxide (10 g.) in 50% ethanol (20 c.c.) was refluxed for 2 hours under nitrogen. The cooled solution was acidified and the yellow-brown solid separated, dried, and recrystallised from toluene as yellow crystals (0·61 g.), m. p. 201°. Repeated crystallisation from toluene raised the m. p. of the *diphenylamine* to 210° (Found: N, 2·9; I, 51·2. $C_{14}H_{11}O_3NI_2$ requires N, 2·8; I, 51·3%).

4'-Hydroxydiphenylamine-4-carboxylic Acid.—A solution of the foregoing acid (1 g.) in glacial acetic acid (5 c.c.) and hydriodic acid (constant-boiling; 3·3 c.c.) was boiled for 1 hour. The solution, which became very dark owing to evolution of iodine, was diluted with water and extracted with ether. The extract was washed with water, sodium hydrogen sulphite solution, sodium hydrogen carbonate solution, and water. The ether was evaporated, to leave the *acid* which, crystallised from a large volume of water, had m. p. 226° (0·22 g.), unchanged after recrystallisation from aqueous acetic acid (Found: C, 68·1; H, 4·95; N, 6·05. $C_{13}H_{11}O_3N$ requires C, 68·1; H, 4·85; N, 6·1%).

Methyl 2 : 6-Di-iodo-4'-methoxydiphenylamine-4-carboxylate.—2 : 6-Di-iodo-4'-methoxydiphenylamine-4-carboxylic acid (0·80 g.) was heated in methanol (10 c.c.) and saturated with hydrogen chloride for 10 minutes. Evaporation left an oily *ester* which was redissolved in methanol and precipitated on the addition of water as a pale yellow solid. Chromatography on alumina in ether and two crystallisations from *cyclo*hexane gave colourless crystals (0·53 g.), m. p. 111° (Found: C, 35·4; H, 2·6; N, 2·85; I, 50·05. $C_{15}H_{13}O_3NI_2$ requires C, 35·4; H, 2·6; N, 2·75; I, 49·85%).

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131. *Nucleophilic Displacement of Fluorine from Aromatic Compounds. Part I.*

By C. W. L. Bevan.

Arrhenius parameters have been determined over a range of temperatures for the reactions of a series of *o*-fluoronitrobenzenes substituted in the *para*-position to the fluorine with sodium ethoxide in absolute ethyl alcohol. An earlier tentative suggestion that the order of mesomeric release from the halogens is I>Br>Cl>F is invalidated by the results: these are briefly discussed in the light of those obtained recently in a similar reaction.

Bevan (*J.*, 1951, 2340) suggested that the sequence of halogen reactivity towards nucleophilic reagents, in the *p*-halogenonitrobenzenes, might be explained in terms of a mesomeric release from halogen atoms in the order I>Br>Cl>F. To test this, and to investigate the effect of both activating and deactivating substituents on nucleophilic replacement at an aromatic carbon atom, Arrhenius parameters have been determined, in absolute alcohol, for the reaction

where R is NH_2, H, F, Cl, Br, I, or NO_2. The effects of these and other substituents R on the reaction of analogous bromides with piperidine have been determined by Berliner and Monack (*J. Amer. Chem. Soc.*, 1952, **74**, 1574), who assumed, as is done in the present paper, that the effect of the *o*-nitro-group on the reaction rates is a constant factor. Rate constants are assembled in Table 1.

Table 1. k_2 *in l. sec.*$^{-1}$ *mole*$^{-1}$ *for 4-substituted 1-fluoro-2-nitrobenzenes with* OEt^- *in absolute ethanol.*

R = NH_2		R = H		R = F	
Temp.	k_2	Temp.	k_2	Temp.	k_2
89·63°	$6{\cdot}70 \times 10^{-3}$	60·98°	$2{\cdot}86 \times 10^{-2}$	60·98°	$4{\cdot}80 \times 10^{-3}$
69·30	$8{\cdot}53 \times 10^{-4}$	49·62	$9{\cdot}88 \times 10^{-3}$	50·98	$1{\cdot}90 \times 10^{-3}$
49·56	$9{\cdot}02 \times 10^{-5}$	40·36	$3{\cdot}86 \times 10^{-3}$	40·98	$7{\cdot}00 \times 10^{-3}$
		31·80	$1{\cdot}55 \times 10^{-3}$	22·10	$8{\cdot}71 \times 10^{-4}$
R = Cl		R = I		R = Br	
Temp.	k_2	Temp.	k_2	Temp.	k_2
51·05°	$1{\cdot}39 \times 10^{-1}$	49·76°	$1{\cdot}66 \times 10^{-1}$	50·98°	$1{\cdot}90 \times 10^{-1}$
36·60	$3{\cdot}68 \times 10^{-2}$	41·29	$8{\cdot}02 \times 10^{-2}$	40·98	$7{\cdot}99 \times 10^{-2}$
0·25	$7{\cdot}49 \times 10^{-4}$	30·18	$2{\cdot}91 \times 10^{-2}$	30·98	$3{\cdot}24 \times 10^{-2}$
		20·83	$1{\cdot}15 \times 10^{-2}$	22·10	$1{\cdot}35 \times 10^{-2}$

For 1-fluoro-2 : 4-dinitrobenzene it was not possible to determine Arrhenius parameters because the reaction was too fast. The rate constant at −20·22° was 16·6 l. sec.$^{-1}$ mole^{-1}. Backwith, Miller, and Leahy (*J.*, 1952, 3552) estimate E for this reaction with OMe^- as 14·35 kcal.; Bevan (*loc. cit.*) gives E for reaction of *p*-fluoronitrobenzene with OEt^- as 19·0 kcal., and Bye (unpublished results) gives E for the reaction with OMe^- as 20·3 kcal.; it is therefore assumed that E for reaction of 1-fluoro-2 : 4-dinitrobenzene with OEt^- is 14·35 − (20·3 − 19·0) = 13 kcal., giving k_2 at 49·6° = *ca.* $4{\cdot}57 \times 10^3$ l. sec.$^{-1}$ mole^{-1}.

The sequence of rates in Table 2 shows that, as *para*-substituents in the reaction studied, all the halogens are activating with respect to hydrogen; *i.e.*, they withdraw aromatic electrons from the benzene ring and they do so in the order I∼Br>Cl⩾F. Since the (−*I*) effects of the halogens are undoubtedly in the order F>Cl>Br>I, the results indicate a mesomeric release in the order F⩾Cl>Br∼I.

It may be noted that Berliner and Monack (*loc. cit.*) found a *p*-fluoro-atom to be de-

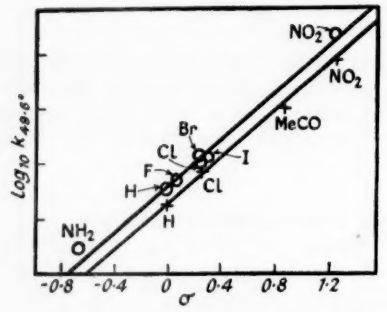
activating in the reaction of *o*-bromonitrobenzene with piperidine, giving an activation energy ~1·2 kcal. higher than in the parent compound. However, in the closely similar case studied here over a range of temperatures, *p*-fluorine was slightly activating and led to a value of *E* the same as in the parent compound. Further, the difference in reactivity

TABLE 2. *k_2 in l. sec.$^{-1}$ mole^{-1} at 49·6° and Arrhenius parameters ($k_2 = Be^{-E/RT}$).*

p-Subst.:	NH_2	H	F	Cl	I	Br	NO_2
k_2	$9{\cdot}02 \times 10^{-5}$	$9{\cdot}88 \times 10^{-3}$	$1{\cdot}66 \times 10^{-2}$	$1{\cdot}15 \times 10^{-1}$	$1{\cdot}65 \times 10^{-1}$	$1{\cdot}68 \times 10^{-1}$	$4{\cdot}6 \times 10^{3}$
$\log_{10} B$	10·7	11·7	11·9	11·4	11·0	11·0	—
E (± 0·15 kcal.)	25·0	20·1	20·1	18·2	17·4	17·4	[13·0]

between the parent compound and the *p*-amino-compound is here of the order of 10^2 which shows a much smaller deviation from the behaviour in non-activated substitution (cf. Badger, Cook, and Vidal, *J.*, 1947, 1109) than was exhibited by a *p*-amino-group in the reaction studied by Berliner and Monack (*loc. cit.*).

The plot of $\log_{10} k$ at 49·6° against Hammett's σ values (Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, 1940, Chapter VIII) gives a line of slope ~3·3, indicating that this is a reaction which is considerably less susceptible to the influence of *p*-substituents than is the reaction between *o*-bromonitrobenzene and piperidine.



○, *Present investigation*; +, *Bunnett* et al. (loc. cit.).
Plot of Hammett's σ against $\log_{10} k_{49\cdot6}$.

This is probably connected with the much greater nucleophilic power of OEt^- than of piperidine, and explains the greater effect of a *p*-amino-group in the latter case.

The figure further revealed that when the determined rate constant is used for 1-fluoro-2 : 4-dinitrobenzene and *E* is assumed to be 13·0 (see above), the *p*-nitro-compound falls close to the line if the phenolic constant of 1·27 is assumed. This is confirmed by a similar plot of the relative rates given by Bunnett *et al.* (*Chem. Reviews*, 1951, **49**, 309) and the results of Berliner and Monack (*loc. cit.*). The *p*-amino-group falls well off the line, as expected, and it is probably fortuitous that the *p*-nitro-group falls near the line since both these groups so powerfully perturb the benzene ring as to make it surprising that they should conform to a close log plot as they do in so many side-chain reactions.

EXPERIMENTAL

Materials.—All compounds used in rate measurements were crystallised to constant m. p. from the appropriate solvent.

4-*Amino*-1-*fluoro*-2-*nitrobenzene*. *p*-Fluoronitrobenzene obtained by nitration of fluorobenzene was reduced with iron dust and dilute hydrochloric acid. The resulting *p*-fluoraniline was nitrated (Holleman and Beekman, *Rec. Trav. chim.*, 1904, **23**, 237); the product had m. p. 98°.

Fluoronitrobenzene. Fluorobenzene was nitrated by Swarts's method (*Rec. Trav. chim.*, 1914, **33**, 263) and fractionated, to give a product, b. p. 112°/22 mm., m. p. −5·3°.

1 : 4-*Difluoro*-2-*nitrobenzene*. By Schiemann's method (*Ber.*, 1929, **62**, 3040) *p*-fluoroaniline was converted into *p*-difluorobenzene, which was nitrated by Swarts's method (*Bull. Acad. Roy. Belg.*, 1913, 241). The product had b. p. 103°/25 mm., m. p. −12°.

4-Chloro-1-fluoro-2-nitrobenzene. Prepared from 4-amino-1-fluoro-2-nitrobenzene (Swarts, *Rec. Trav. chim.*, 1916, **35**, 131), this had m. p. 10°.

4-Bromo-1-fluoro-2-nitrobenzene. Prepared from 4-amino-1-fluoro-2-nitrobenzene (Hove, *Bull. Acad. Roy. Belg.*, 1927, **1**, 372), this had m. p. 19°.

1-Fluoro-4-iodo-2-nitrofluorobenzene. Prepared from 4-amino-1-fluoro-2-nitrobenzene (Hove, *ibid.*, p. 1), this had m. p. 35·5°.

1-Fluoro-2 : 4-dinitrobenzene. A commercial specimen, recrystallised from ether, had m. p. 26°.

Ethyl alcohol was dried and stored, as described previously (Bevan, *loc. cit.*).

Product Analyses.—Aliquots of reaction mixture which had been allowed to go to completion were concentrated and acidified with hydrochloric acid, and the crystals deposited were washed with a little water and dried, giving the corresponding 4-halogeno-2-nitrophenetoles. 4-Fluoro-, m. p. 33° (lit., 33·7°), 4-chloro-, m. p. 60° (lit., 61°), 4-bromo-, m. p. 57°, and 4-iodo-derivatives, m. p. 77° (lit., 80°), were identified. The reactions followed a second-order rate law and gave good constants over 5% to 95% reaction; therefore from the above figures the product was evidently the corresponding phenetole.

Kinetic Measurements.—In all cases, except that of 1-fluoro-2 : 4-dinitrobenzene, sodium ethoxide was ~0·033M and halide ~0·025M. In the exceptional case both concentrations were reduced by a factor of 10. For 4-amino-1-fluoro-2-nitrobenzene sealed tubes were used. Otherwise 50 ml. of a solution of the halide, to be 0·025M on dilution with 25 ml. of sodium ethoxide (~0·1M), were brought to the thermostat temperature in a stoppered flask. The sodium ethoxide, also at thermostat temperature, was added from a fast-delivery pipette stored at this temperature. The time of half addition was taken as the time of initial reaction. Aliquots were transferred, by means of a pipette stored at thermostat temperature, into excess of standard hydrochloric acid and back-titrated with standard carbon-dioxide-free alkali in nitrogen, with bromothymol-blue as indicator. Rate constants were calculated from the usual formula for a bimolecular reaction. The results of typical experiments are shown in Table 3. A correction was applied for solvent expansion. Rate constants could be duplicated within 1%.

TABLE 3. *Determination of rate constants* k_2 (*l. sec.*$^{-1}$ *mole*$^{-1}$).

Reaction of 4-amino-1-fluoro-2-nitrobenzene with sodium ethoxide in absolute ethyl alcohol.

Initially, [Halide] ~0·025M and [NaOEt] ~0·033M. Concns. are expressed in ml. of 0·00893N-NaOH per 4·90-ml. sample. Temp., 89·63°.

t (min.)	0	25	32	35	41	45	51	56	65	80	91	105	119
[NaOEt]	16·67	14·25	13·65	13·41	13·01	12·91	12·55	12·31	11·84	11·18	10·71	10·38	9·90
[Halide]	10·72	8·30	7·70	7·46	7·06	6·96	6·60	6·36	5·89	5·23	4·76	4·43	3·95
10^3k_2	—	6·15	6·34	6·41	6·40	6·06	6·08	6·03	6·10	6·13	6·26	6·01	6·18

Mean 6·18; duplicate 6·12; $k_2 = 6·15 \times 10^{-3}$; corr. for solvent expansion (20—90°), $k_2 = 6·69 \times 10^{-3}$.

Reaction of 1 : 4-difluoro-2-nitrobenzene with sodium ethoxide in absolute ethyl alcohol.

Initially, [Halide] ~0·025M and [NaOEt] ~0·033M. Concns. are expressed in ml. of 0·01048N-NaOH per 5·00-ml. sample. Temp., 60·98°.

t (min.)	0	3	5	7·4	10·3	13·28	16	18·87	23·95	27·89	32·8	38·5
[NaOEt]	17·11	14·11	12·68	11·27	10·17	9·24	8·59	8·09	7·37	6·95	6·52	6·19
[Halide]	12·57	9·57	8·06	6·73	5·63	4·70	4·05	3·55	2·83	2·41	1·98	1·65
10^2k_2	—	4·67	4·86	4·90	4·81	4·96	4·86	4·67	4·75	4·83	4·83	4·61

Mean 4·80; duplicate 4·79; $k_2 = 4·80 \times 10^{-2}$.

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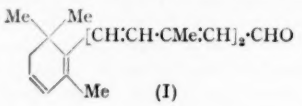
132. *Studies in the Polyene Series. Part XLV.** C_{23}, C_{25} *and* C_{43} *Ketones derived from Retinene*$_1$.

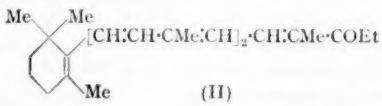
By J. C. Hamlet, H. B. Henbest, and V. Thaller.

The compound obtained by Oppenauer oxidation of vitamin A_1 with diethyl ketone as hydrogen acceptor (which other workers suggested was dehydroretinene$_1$) has been obtained crystalline and shown to be a C_{25} ketone (II). Condensation of retinene$_1$ and acetone leads to the formation of crystalline C_{23} and C_{43} ketones.

A dehydroretinene$_1$ structure (I) was proposed by Haworth, Heilbron, Jones, Morrison, and Polya (*J.*, 1939, 128) for a carbonyl compound obtained by Oppenauer oxidation of vitamin A_1 (or of retinene$_1$; Morton, Salah, and Stubbs, *Nature*, 1947, **159**, 744) in the presence of diethyl ketone. This structure was suggested chiefly on the basis of light-absorption properties, the analysis of a crystalline oxime, and the fact that no geronic acid was isolated on ozonolysis. When crystalline retinene$_2$ [correctly represented by (I)] and derivatives were prepared from synthetic vitamin A_2 (Farrar, Hamlet, Henbest, and Jones, *J.*, 1952, 2657), differences in physical properties made it certain that the Oppenauer product must have been incorrectly formulated.



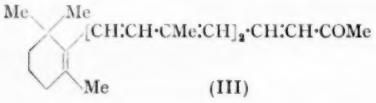
(I)



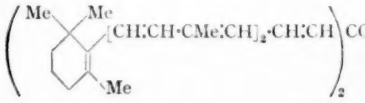
(II)

Repetition of the oxidation experiment followed by chromatography and low temperature crystallization of the chief reaction product afforded a crystalline compound exhibiting light absorption similar to that of the material of Haworth *et al.* This formed a crystalline oxime in good yield and analytical data on the two compounds indicated a $C_{25}H_{36}O$ formula for the parent compound. This would then be represented by the structure (II), being formed by condensation between diethyl ketone and the initially produced retinene$_1$. The position of $\lambda_{max.}$ and the high intensity (relative to retinene$_1$ and retinene$_2$) were in agreement with those expected for a compound with structure (II), and very similar to those recorded with the related C_{23} ketone (see below). An intense band near 1240 cm.$^{-1}$ in the infra-red spectrum indicated a ketonic rather than an aldehydic structure—from the data presented previously (*J.*, 1952, 2657) it was apparent that ketones, but not aldehydes, in this series exhibit such a band in the infra-red region.

The formation of the C_{25} ketone is thus analogous to the synthesis of the C_{23} ketone (III) by Oppenauer oxidation of vitamin A_1 with acetone (Batty, Burawoy, Harper, Heilbron, and Jones, *J.*, 1938, 175). This reaction has been reinvestigated and the C_{23} ketone obtained crystalline (cf. Karrer and Eugster, *Helv. Chim. Acta*, 1951, **34**, 1805); it has also been prepared by condensing retinene$_1$ itself with acetone in the presence of aluminium *tert.*-butoxide, or better, sodium ethoxide.



(III)



(IV)

In the course of purifying the crude C_{23} ketone reaction products by chromatography it was observed that a fairly strongly adsorbed violet band was always present. This was shown to be due to the presence of a C_{43} ketone (IV) by comparison with crystalline material prepared by condensing retinene$_1$ with C_{23} ketone in the presence of alkali. As would be expected, the carbonyl group of this highly unsaturated cross-conjugated ketone was rather unreactive, no oxime being formed under the usual conditions. The relatively

* Part XLIV, *J.*, 1952, 4089.

low frequency and intensity of the carbonyl stretching vibration in the infra-red spectrum also indicated that the carbon–oxygen bond was tending towards a dipolar link ($>\overset{+}{C}-\overset{-}{O}$) (cf. data on *cyclo*heptatrienone, etc., given in the Experimental section), the positive charge being " spread out " into the unsaturated system by hyperconjugation.

Experimental

The general experimental directions are as given by Farrar, Hamlet, Henbest, and Jones (*loc. cit.*).

4 : 7 : 11-*Trimethyl*-13-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*trideca*-4 : 6 : 8 : 10 : 12-*pentaen*-3-*one* (C_{25} *Ketone*) (II).—Vitamin A_1 (2 g.), aluminium *tert.*-butoxide (2·4 g.), diethyl ketone (10 g.), and dry " AnalaR " benzene (70 c.c.) were heated under reflux for 48 hours. Aqueous tartaric acid was added to the cooled mixture, and the benzene layer was separated, washed with water, and dried (Na_2SO_4). After removal of the solvent under reduced pressure the residue was chromatographed in pentane on alumina (300 g.) (deactivated with water, 10%). A single, large, orange band separated from dark material held near the top of the column. Elution of this orange band and removal of solvent gave an orange-red oil (1·34 g.), a portion (0·4 g.) of which was crystallized from pentane at −30°. One crystallization gave solid, m. p. 61—63°; a second crystallization from pentane afforded the *ketone* as orange cubes, m. p. 65—66°, changing at this m. p. to needles, m. p. 80—81° (Found : C, 85·6; H, 10·6. $C_{25}H_{36}O$ requires C, 85·15; H, 10·3%). Ultra-violet absorption : Max. 4000 Å; $\varepsilon = 56{,}800$ (for the liquid product, Haworth *et al.*, *loc. cit.*, give $\lambda_{max.}$ 4010 Å, $\varepsilon = 40{,}600$). Infra-red spectrum : main peaks at 1659 (C:O stretching), 1563 (C:C stretching), 1242, and 962 cm.$^{-1}$.

The crude ketone (0·54 g.) was converted into the oxime as described for retinene$_2$ oxime (*J.*, 1952, 2668). The yield after one crystallization from methanol was 0·31 g.; further recrystallization gave the *oxime* as yellow needles, m. p. 180—181° (Found : C, 81·5; H, 10·05; N, 4·1. $C_{25}H_{37}ON$ requires C, 81·7; H, 10·15; N, 3·8%). Ultra-violet absorption : Max. 3820 Å; $\varepsilon = 73{,}200$ (Haworth *et al.* record m. p. 176—177°; $\lambda_{max.}$ 3860 Å; $\varepsilon = 73{,}500$).

6 : 10-*Dimethyl*-12-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*dodeca*-3 : 5 : 7 : 9 : 11-*pentaen*-2-*one* (III) (C_{23} *Ketone*).—This was prepared by Karrer and Eugster's procedure (*loc. cit.*). The crude total product exhibited $\lambda_{max.}$ 4050 Å ($E^{1\%}_{1\,cm.}$ ~1050) corresponding to about 60% of C_{23} ketone. After the Girard separation, the ketonic fraction was chromatographed on alumina (deactivated with 10% of water), the main fraction affording a solid product (0·61 g. from 2 g. of vitamin A_1 acetate). Crystallization from light petroleum (b. p. 40—60°) gave the red C_{23} ketone, m. p. 103—105·5° (Found : C, 85·25; H, 9·8. Calc. for $C_{23}H_{32}O$: C, 85·15; H, 9·95%). Ultra-violet absorption : Max. 4060 Å; $\varepsilon = 54{,}200$ (Karrer and Eugster give m. p. 105—106°; $\lambda_{max.}$ 4010 Å; $\varepsilon = 53{,}500$). Infra-red spectrum : main peaks at 1680 and 1660 (C:O stretching), 1590 and 1560 (C:C stretching), 1250, and 970 cm.$^{-1}$. If the Girard treatment was omitted, and the ketone purified solely by chromatography,* the m. p. after crystallization was somewhat lower (91—94°) and the crystals were orange-yellow. The lower m. p. probably reflects the presence of one or more (less stable) stereoisomers, which are converted by Girard treatment into the higher-melting, presumably all-*trans*-form—the absorption spectrum of the orange-yellow material ($\lambda_{max.}$ 4060 Å; $\varepsilon = 53{,}200$) was very similar to that of the red form of the ketone.

The *oxime*, prepared from ketone of m. p. 103—105·5°, crystallized from methanol as yellow prisms, m. p. 148—150° (Found : C, 81·3; H, 9·5. $C_{23}H_{33}ON$ requires C, 81·35; H, 9·8%). Ultra-violet absorption : Max. 3850 Å; $\varepsilon = 74{,}600$.

Di*-[4 : 8-*dimethyl*-10-(2 : 6 : 6-*trimethyl*cyclo*hex*-1-*enyl*)*deca*-1 : 3 : 5 : 7 : 9-*pentaenyl*] *Ketone (C_{43} *Ketone*) (IV).—Ethanol (2 c.c.) containing dissolved sodium (25 mg.) was added to a solution of retinene$_1$ (0·153 g.) and C_{23} ketone (0·154 g.) in benzene (10 c.c.), and the mixture was stirred at 10° for 50 minutes. Light petroleum and aqueous tartaric acid were added and the organic layer was separated and evaporated under reduced pressure. The residue was chromatographed in light petroleum on alumina (150 g., deactivated with 20% of water), development being effected with ether–light petroleum (1 : 50). The dark violet zone was cut out and the C_{43} ketone eluted from it with ether. A single crystallization from light petroleum gave fairly pure ketone (0·155 g., 50%), m. p. 106—122°. For further purification, the total crude material (0·18 g.) was combined and rechromatographed on deactivated alumina. Three small red zones, one above and two below, were separated from the violet zone and were

* A deep violet band near the top of the column was eluted separately; this material showed light-absorption properties identical with those of the C_{43} ketone described below.

rejected. The main zone gave, after crystallization from light petroleum (b. p. 40—60°), crystals (0·12 g.) with m. p. 111—117°. Recrystallization from the same solvent afforded C_{43} *ketone*, m. p. 118—122° (softening at 105°) (Found: C, 87·1; H, 10·1. $C_{43}H_{58}O$ requires C, 87·4; H, 9·9%). Ultra-violet absorption (in dioxan): Max. 4680 Å; $\varepsilon = 72{,}000$. Infra-red spectrum: main peaks at 1635 (C:O stretching), 1585 and 1555 (C:C stretching), 1070, and 965 cm.$^{-1}$. The low value of the carbonyl stretching frequency may be compared with those recorded for *cyclo*heptatrienone (1638 cm.$^{-1}$; von Doering and Detert, *J. Amer. Chem. Soc.*, 1951, **73**, 876), tropolone (1615 cm.$^{-1}$, Koch, *J.*, 1951, 512), and β-methyltropolone methyl ether (1630 cm.$^{-1}$; Haworth and Hobson, *J.*, 1951, 561).

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133. *The Chemistry of Bivalent Germanium Compounds. Part III.* The Polarographic Behaviour of Bivalent Germanium.*

By D. A. EVEREST.

The reduction and oxidation of bivalent germanium at the dropping-mercury electrode have been studied in hydrochloric and in hypophosphorous acid solution. The behaviour observed supported the postulate that the electrode reaction involved the Ge^{++} ion although bivalent germanium probably entered into complex formation with both solvents.

A CATHODIC wave, due to the reduction Ge(II) ⟶ Ge, has been found in 6N-hydrochloric acid by Alimarin and Ivanov-Emin (*J. Gen. Chem., U.S.S.R.*, 1944, **17**, 204). The half-wave potential ($E_{\frac{1}{2}}$) was approximately −0·5 v in 6N-hydrochloric acid (relatively to the mercury pool anode), $E_{\frac{1}{2}}$ moving to more positive values on increase in the germanium concentration or on decrease of that of the hydrochloric acid. An anodic wave, due to the oxidation Ge(II) ⟶ Ge(IV), has been observed by Cozzi and Vivarelli (*Mikrochem. Mikrochim. Acta*, 1951, **36/37**, 594), who found that this wave was obscured by that due to the chloride ion if the concentration of the latter exceeded 2N; this interference was reduced on addition of cadmium sulphate, which removed some of the chloride ions by formation of complexes such as $CdCl_4^{--}$.

The present investigation has been carried out in two solvents, hydrochloric and hypophosphorous acids, and the results will be considered under these two headings.

Effect of concentrations of germanium and of acid.

Hydrochloric acid solutions.

	3·1N-HCl		Ge concn., 2·43 × 10^{-3}M			
Ge concn., 10^{-3}M	$E_{\frac{1}{2}}$, anodic	$E_{\frac{1}{2}}$, cathodic	Acid, N	$E_{\frac{1}{2}}$, anodic	$E_{\frac{1}{2}}$, cathodic	D.C.C.
2·39	—	−0·49	3·54	—	−0·51	3·21
3·23	—	−0·49	2·82	—	−0·475	3·30
3·31	—	−0·49	2·74	—	−0·46	3·21
3·58	—	−0·485	1·63	—	−0·43	2·38
4·96	—	−0·48	1·09	—	−0·42	2·20
6·89	—	−0·47	0·55	—	−0·42	1·47

Hypophosphorous acid solutions.

	3·9N-H_3PO_2		Ge concn., 2·09 × 10^{-3}M			
1·21	−0·175	−0·57	3·82	−0·17	−0·565	—
2·36	−0·17	−0·565	3·11	−0·175	−0·565	—
3·37	−0·175	−0·575	2·64	−0·185	−0·55	—
4·47	−0·17	−0·57	1·67	−0·185	−0·55	—
4·81	−0·17	−0·575	1·19	−0·19	−0·54	—
6·11	−0·17	−0·57	0·96	−0·19	−0·53	—

* Part II, *J.*, 1952, 1670.

Experimental

Apparatus.—A photographically recording Cambridge polarograph was used for the main part of this work; measurements, except where otherwise stated, were made relative to the saturated calomel electrode (S.C.E.). The $m^{\frac{2}{3}}t^{\frac{1}{6}}$ factors for the capillaries were measured in 0·1N-potassium chloride on open circuit and had values of 1·021, 1·470, 1·669, and 2·699 (see p. 662).

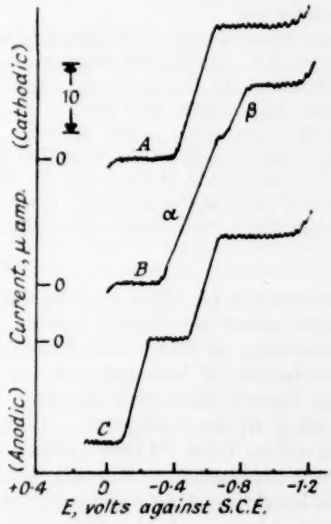
Procedure.—For the experiments in hydrochloric acid, germanium dioxide (0·1—0·2 g.) was accurately weighed and reduced to the bivalent state by heating it to 100° for 1 hour with 3N-hydrochloric acid (32·5 ml.) and 50% hypophosphorous acid (2·5 ml.); 25% hypophosphorous acid (35 ml.) was used for the reduction in the chloride-free experiments. These were used as stock solutions, known volumes of which were accurately diluted to the required concentration.

It was not found necessary to deoxygenate the solutions used, their strongly reducing character removing any dissolved oxygen present, and any loss of bivalent germanium thereby incurred being negligible at the concentrations used (1—9 × 10^{-3}M). If the polarographic

Wave A. Ge *concn.*, 3·58 × 10^{-3}M; $m^{\frac{2}{3}}t^{\frac{1}{6}}$ = 1·669; *solvent*, 3·1N-HCl.

Wave B. Ge *concn.*, 8·26 × 10^{-3}M; $m^{\frac{2}{3}}t^{\frac{1}{6}}$ = 1·021; *solvent*, 4·3N-HCl.

Wave C. Ge *concn.*, 4·47 × 10^{-3}M; $m^{\frac{2}{3}}t^{\frac{1}{6}}$ = 1·669; *solvent*, 3·9N-H_3PO_2.



runs were carried out rapidly, an inert atmosphere was not found essential, bivalent germanium being fairly stable in air, especially in presence of hypophosphorous acid. The reliability of this procedure was shown by the constancy of the diffusion current constant (D.C.C.) values obtained from different experiments. All runs were carried out at 25°.

Results.—Hydrochloric acid. Well-defined cathodic waves were obtained (Wave *A*, Fig.), exhibiting maxima which could be suppressed by addition of 0·005—0·008% of methyl cellulose which had no effect upon the magnitude of the diffusion current. It was found, in agreement with Alimarin and Ivanov-Emin (*loc. cit.*), that $E_{\frac{1}{2}}$ moved to more positive values on decrease of hydrochloric acid concentration or on increase of that of the germanium (see Table). If a mercury pool anode was used (cf. *idem, ibid.*) the $E_{\frac{1}{2}}$ values were more positive than when measured against the S.C.E. (*e.g.*, −0·33 v in 4·3N-hydrochloric acid as against the S.C.E. value of −0·47 v in 3·1N-hydrochloric acid; germanium concentration 6·8 × 10^{-3}M); the mercury anode had a potential of about −0·15 to −0·2 v against the S.C.E. Similar behaviour was found by Smyz (*Rec. Trav. chim.*, 1925, **44**, 580) in the electrolysis of stannous salts, the mercury anode acquiring a potential of about −0·15 v against the S.C.E. The decrease in the D.C.C. with decreasing acid concentration (see Table) was probably due to hydrolysis which reduced the effective germanium concentration. As reported by Alimarin and Ivanov-Emin (*loc. cit.*), metallic germanium was the reduction product in both hydrochloric and hypophosphorous acids, *i.e.*, n (the number of electrons in the reduction) = 2.

When the germanium concentration was increased above a certain value, depending upon

the $m^{\frac{1}{3}}t^{\frac{1}{6}}$ factor, the cathodic wave split into two parts (α and β, wave B); the first wave (α) had a constant height, but the second (β) increased with increasing germanium concentration. The germanium concentrations at which splitting occurred were: 6·20, 10·1, and 14·0 $\times$ 10^{-3}M in 4·3N-hydrochloric acid, and 9·1 $\times$ 10^{-3}M in 3·1N-hydrochloric acid, the corresponding $m^{\frac{1}{3}}t^{\frac{1}{6}}$ factors being 1·021, 1·470, 2·699, and 1·669. The overall D.C.C. for the double wave ($\alpha + \beta$) was 3·42 $\pm$ 0·02 as compared with 3·22 $\pm$ 0·02 for the ordinary single wave obtained below the splitting concentration (*e.g.*, wave *A*, Fig.), thus making $n = 2{\cdot}13$ for the overall double-wave. This value was sufficiently near to 2 to show that the double wave ($\alpha + \beta$) was due only to reduction to elementary germanium, and that no new reduction products were formed. This behaviour was similar to that observed by Lingane and Niedrach in the polarographic reduction of quadrivalent selenium and tellurium (*J. Amer. Chem. Soc.*, 1949, **71**, 196). A probable explanation, based on that advanced by these authors, was that the constancy of the first wave height was due to the formation of a film of elementary germanium on the surface of the mercury drop, and that this interfered with the electrode reaction, causing further deposition to occur at more negative potentials.

The anodic wave observed by Cozzi and Vivarelli (*loc. cit.*) has been confirmed; it has been studied chiefly in hypophosphorous acid solution because the chloride of the hydrochloric acid caused interference.

Hypophosphorous acid. With this acid as solvent (total acid maintained at 3·5N, germanium concentration 2·4 $\times$ 10^{-3}M) the values of $E_{\frac{1}{2}}$ (cathodic) moved to more negative values ($-0{\cdot}51$ to $-0{\cdot}565$) whilst the D.C.C. changed from 3·22 $\pm$ 0·02 to 2·03 $\pm$ 0·04. Both the anodic and the cathodic waves were well defined in hypophosphorous acid (Wave C, Fig.), the D.C.C. for the anodic wave being $-2{\cdot}01 \pm 0{\cdot}03$. The effects of the concentrations of germanium and of hypophosphorous acid on the $E_{\frac{1}{2}}$ values are shown in the Table, these two factors having no effect on the magnitude of either D.C.C. values. As in hydrochloric acid, the cathodic waves split into two parts above a certain germanium concentration. The behaviour of these split waves was similar to that shown in hydrochloric acid.

Discussion

Hydrochloric Acid.—The positive shift of $E_{\frac{1}{2}}$ (cathodic) with decreased hydrochloric acid concentration (see Table) was consistent with reduction involving the Ge^{++} ion, the concentration of which would decrease with increased chloride concentration owing to the formation of ions such as $GeCl_3^-$. Analogous behaviour has been found by Riccoboni, Popoff, and Arich (*Gazzetta*, 1949, **79**, 547) in the polarographic reduction of stannous salts, $E_{\frac{1}{2}}$ decreasing from $-0{\cdot}54$ to $-0{\cdot}45$ v on decrease of the chloride concentration from 4·0 to 0·1M. These authors considered that it was the Sn^{++} ion which was reduced, the concentration of which would be similarly decreased with increasing chloride concentration owing to formation of chloro-complexes.

Hypophosphorous Acid.—The cathodic reaction in hypophosphorous acid also presumably involved the simple Ge^{++} ion. The more negative values of $E_{\frac{1}{2}}$ (cathodic) in hypophosphorous compared with hydrochloric acid, at any given germanium and acid concentration, probably indicated complex formation between bivalent germanium and hypophosphorous acid. This hypothesis was supported by the negative shift of $E_{\frac{1}{2}}$ (anodic) and positive shift of $E_{\frac{1}{2}}$ (cathodic) with decreasing hypophosphorous acid concentration (see Table). Insufficient is known, however, about complexes involving hypophosphorous acid for any definite conclusions to be drawn. The similarly of the D.C.C. values for the anodic and cathodic waves ($-2{\cdot}01 \pm 0{\cdot}03$ and $2{\cdot}03 \pm 0{\cdot}04$) indicated that the same entities were involved in both anodic and cathodic processes.

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134. *The Adaptation of Some* Bact. coli *Strains to Utilise Sucrose.*

By N. M. Mims and Sir Cyril Hinshelwood.

Two strains of *Bact. coli*, initially showing very long lags and slow growth rates, on transfer to a medium with sucrose as the carbon source become adapted to grow without lag and at an optimum rate not only by serial subculture in a sucrose medium but also by long-continued passage through glucose. The disappearance of the lag in the sucrose is attended by the nearly simultaneous attainment of a further stage in the adaptation to glucose.

The fact that towards the end of the lag in sucrose considerable increases in cell mass without multiplication of numbers occurs, taken in conjunction with other kinds of evidence, shows that this is not a case of mutation and selection, but of adaptations where the glucose- and sucrose-utilising mechanisms are partially linked.

The well-known capacity of bacterial cells to develop increased powers of assimilating carbon sources such as sugars when repeatedly cultured in their presence is not only explicable in terms of two alternative hypotheses, but may possibly even depend upon the one or the other of two corresponding mechanisms according to circumstances. These are, as repeatedly discussed in the literature, on the one hand, direct modification of enzymatic constitution, when the cell substance is continuously synthesised in new media, and, on the other hand, chance mutations in parts of the cell material which give new forms selectively favoured by the appropriate environment. Before a satisfactorily clear idea can be formed of the relative importance of the two modes of response, extensive experimental results are needed. This paper describes investigations on the adaptation of some strains of *Bact. coli*.

Adaptation of Two Strains of Bact. coli *to Sucrose.*—One strain (g) was an *Escherichia coli* obtained from the National Collection of Type Cultures, and the other (b) was obtained from Dr. R. L. Vollum (Radcliffe Infirmary, Oxford). Both required a training process (gradual elimination of an asparagine enrichment of the growth medium) before they would grow without lag on transfer from broth to the usual synthetic medium employed in this work (glucose, ammonium sulphate, phosphate buffer, magnesium sulphate, as given by Gladstone, Fildes, and Richardson, *Brit. J. Exp. Path.*, 1935, **16**, 335). The two strains were chosen from a large number tested because they showed on transfer to a medium in which sucrose replaced glucose very long lags, and revealed the need for extensive adaptation to the sucrose.

On serial subculture in the sucrose medium (each subculture corresponding to about ten successive cell divisions) the lag fell eventually to zero, and the mean generation time (time taken for the cell number to double in the logarithmic growth phase, *i.e.*, inverse measure of growth rate), after showing erratic fluctuations, fell to a steady and constant limit. This adjustment process is illustrated for strain (b) in Fig. 1, and resembles that frequently met in previous studies of other examples.

It was observed, however, that if the parent culture in glucose, from which the original transfer to sucrose was made, was continuously subcultured in the glucose medium itself, and at intervals tested by the transfer of samples to sucrose, complete adaptation to the latter sugar was eventually acquired. This, at first sight, might seem to suggest that the serial subculture in glucose was somehow leading to an enrichment of the population with sucrose-utilising mutants, the origin of which was due to chance.

But it was also observed that the sucrose-adaptation was accompanied by the nearly though not quite simultaneous attainment of a further stage of adaptation of the cells to the basal glucose–ammonium sulphate medium itself. This was revealed, not by the lag, which was already zero but by the mean generation time, which quite soon after the appearance of the sucrose adaptation showed a further fall to 40 min. with one of the strains and to 36 min. with the other. These various observations are illustrated in Tables 1 and 2 and in Fig. 2.

Thus there is not only the possibility that sucrose-utilising mutants have appeared, but also the possibility that in the final stages of adaptation to the ammonium sulphate–glucose medium an enzyme has developed which, as well as causing a more efficient metabolism of glucose, is capable of dealing with sucrose.

FIG. 1. *Serial passage through sucrose.*

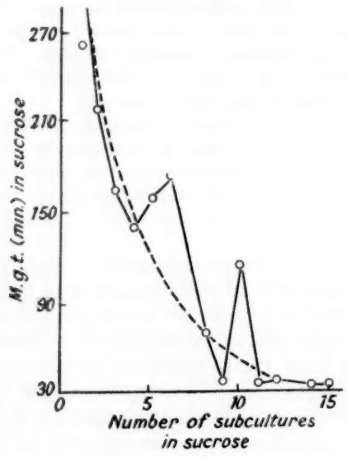
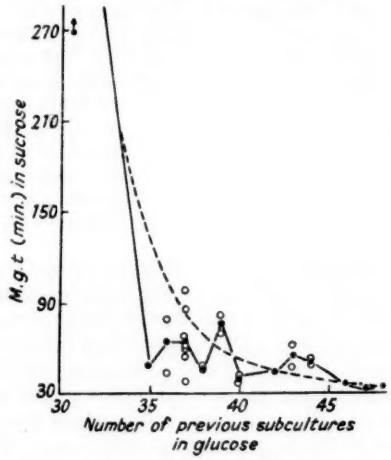


FIG. 2. *Serial passage through glucose.*



○, *individual values*; ●, *average values.*

TABLE 1. *Behaviour of strain (b) on serial passage through glucose.*

Strain (b) is *Bact. coli* (P 81 Type 2); ΔL is the amount by which the lag in sucrose exceeds the (very short) lag in glucose; m.g.t. = mean generation time.

Number of subcultures in glucose preceding test	M.g.t. in glucose, min.	M.g.t. in sucrose, min.	ΔL, hours (or as stated)
1—20	45—59, mean 50	160—354, mean 255	4—10 days
21—35	44—56, mean 50	45—330	214—2
36	54	39, 98, 62, 64, 63, 69, 65, 86, 63, 55	1·0
37	42	48	0·2
38	47	53, 83	1·5
39	41	42	0·5
40	46	45	1·8
42	46	51	2·0
43	42	52	1·2
45	36	36	0·0
46	33	34, 35	0·0
49	36	—	—
Cultures taken from single colonies of subculture 47		35, 34, 34, 35, 36, 34, 34, 34, 35, 34	—

TABLE 2. *Behaviour of strain (g) on serial passage through glucose.*

Strain (g.) is *Escherichia coli* of the National Collection of Type Cultures; ΔL is the amount by which the lag in sucrose exceeds that in glucose; m.g.t. = mean generation time.

Number of subcultures in glucose preceding test	M.g.t. in glucose, min.	M.g.t. in sucrose, min.	ΔL, hours (or as stated)
0	86	340	189
1—10	58 (mean)	75 (mean)	mostly >10 days
11—20	59 (mean)	—	mostly >8 days
21	59	—	<10
22	63	—	<10
23	56	37	0
25	—	38	0
27	44	—	—
29	40	—	—

Bacterial Mass and Bacterial Number.—If growth in sucrose depended upon the presence of mutants formed by chance in previous periods of multiplication, then the lag phase would be simply the time required for these special cells to multiply to a count comparable with the total inoculum. There would then be no detectable increase in the total bacterial mass without a corresponding increase in the cell number. If, on the other hand, the lag phase is the period in which intermediates are slowly accumulated and the steady state of a new series of growth reactions is established, then a large proportion of the cells may begin to increase in mass more or less at the same time, and a considerable synthesis of bacterial substance may precede any detectable multiplication.

Cell numbers are determinable by direct counting in a hæmacytometer chamber under the microscope, and bacterial mass has been shown to be measured by the turbidity of the culture. This has been shown by Monod for *Bact. coli* (" Recherches sur la Croissance des Cultures Bactériennes," Paris, Hermann & Cie, 1942) by direct comparison with dry weights, and by Baskett with the closely related *Bact. lactis aerogenes* (unpublished observations) by comparison with nitrogen content. Even if the proportionality is not linear (which in fact it normally is) the turbidity changes will at the very least show whether the culture as a whole is changing just before division sets in.

The strain (b) of *Bact. coli* was accordingly kept under observation during a long lag phase in the sucrose medium, and the initial stages of growth were studied with results shown in Fig. 3. Here the total bacterial mass for comparative purposes is expressed in terms of an equivalent number of cells of a constant *standard size*. This standard was

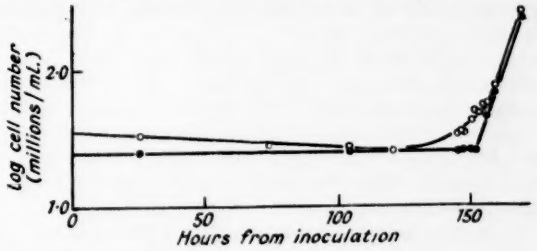


FIG. 3. *Bacterial mass and bacterial cell number.*
○, *mass*; ●, *number.*

taken to correspond to a time near the end of the lag phase. (Since there is a certain shrinkage or decay during the first few days after inoculation with a very inert culture, there is, as shown, a slight downward slope of the mass curve at first.)

It is seen that a considerable increase in mass does in fact precede the multiplication in numbers, and the *prima facie* conclusion is that a general modification of the bulk of the population has been in progress during the lag. If the ultimate growth were to be referred only to a minute proportion of pre-existent mutants, the bulk of the population remaining inert and incapable of multiplication, the general swelling in size which normally precedes division would not take place. The fresh bacterial mass would be undetectable until the mutants reached a detectable count. The general change in the properties of the culture before numbers increase shows that most of the cells are in fact changing in some way. Since wholesale division ensues soon after, the hypothesis that the lag has been a period of chemical change in them all is almost impossible to escape. The mutation hypothesis will only be applicable in this particular example if a minute proportion of mutants present in the culture are assumed able to provide, in the form of diffusible substances, intermediates, or metabolites which can be used by the normal non-mutant bacteria for incorporation into their cell structure. Since, from the length of the lag, the initial number of mutants would be almost vanishingly small, the activity which would have to be ascribed to them would hardly be credible.

Statistical Spread of Growth Rates.—When the culture is fully adapted to sucrose, the growth rate is constant and reproducible, the measured values, for strain (b), of the m.g.t. being 35 ± 1 min. In the intermediate stages the enzymatic organisation of the cell is unstable, and this factor is reflected not only in an irregular fluctuation of the m.g.t. from one subculture to the next, but also in an irreproducibility of behaviour when similar

inocula are transferred to a new batch of medium. When the lag of strain (b) in sucrose had just fallen to about one hour (at a first transfer from glucose) ten culture tubes containing sucrose medium were inoculated with 0·1-ml. samples of the same glucose parent culture. The lag was in each case about one hour, but the ten values of the m.g.t. ranged from 39 to 98 min. (Table 1).

Discussion.—The fact that the cell mass increases before there is any detectable multiplication renders very probable the hypothesis of a general adaptive response of the whole population. If this view is accepted, the conclusion is that the final stages in the adaptation to the glucose–ammonium sulphate medium and the development of the sucrose adaptation are closely coupled.

The violent fluctuations in growth rate which occur just before the stable state is reached would in any event be difficult to account for by the hypothesis of mutation and selection, since as soon as the mutants are established they should show their own stable properties and would not subsequently fluctuate rapidly in numbers. The variations are certainly not due to experimental error, since they disappear as soon as the strain is stabilised, as is shown by the final entries in Table 2. The fluctuations are much more readily explicable by the adaptation theory. At first, the enzymatic organisation of the cell is unstable and slight variations in the conditions, for example in the size or age of the inoculum, lead to different growth characteristics, including the temporary reversions which the mutation theory could hardly explain at all.

To account for the scatter in the actual growth rates of similar inocula referred to in the previous section the mutation theory would have to postulate either a wide variation in the efficiency of existing mutants or a whole range of mutant types with differing growth rates. The first postulate is itself practically equivalent to an adaptation theory, and the second leads to difficulties of a special kind. The scatter would have to be explained by random variations in the numbers and types of mutants transferred in the inoculum. For these to be significant the actual numbers would have to be very small since otherwise a representative sample of all types would be transferred on each occasion. The lags, therefore, would be long. But they are in fact all about one hour, and leave no time for fresh selective processes to operate.

If, on the other hand, we postulate a period of very unstable adjustment in the course of the adaptation, then the behaviour of the various inocula will depend upon the exact amount of glucose or of intermediates carried over with the cells, the degree of thermal shock associated with transfer, the exact conditions of aeration in the new sucrose medium and so on. Thus the non-uniform growth characteristics will be due essentially to the instability of the organisation at the moment when one reaction pattern is in competition with another which is about to replace it.

The partial coupling of the sucrose and glucose adaptations is in itself interesting and is, in a general way, paralleled by some experiments in which *Bact. lactis aerogenes* was trained to glucose and to cellobiose, passage through the one improving the growth rate in the other. Two possibilities suggest themselves. The first is that during the passage through glucose the cells are exposed to minute concentrations of sucrose synthesised by their own enzymes, and so have the opportunity, especially during periods of glucose exhaustion, of metabolising sucrose itself. The second possibility, which is more general, is that during the final stages of adaptation to the glucose–ammonium sulphate medium there is some measure of reorganisation of the enzyme systems and that this is such as to permit an easier development of the sucrose-utilising mechanisms. Such a phenomenon might well prove to be rather common with closely related pairs of sugars.

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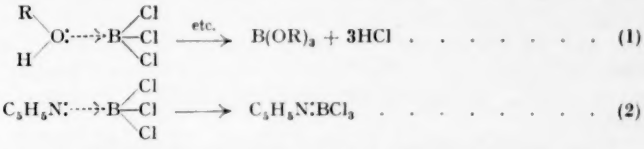
135. *Reaction Sequences in Alcohol–Boron Trichloride–Pyridine Systems.*

By M. F. Lappert.

Addition of boron trichloride (1 mol.) to alcohols (the isomeric butanols, octan-1-ol, octan-2-ol, and 1-phenylethanol) (3 mols.) in presence of pyridine (3 mols.) at $-10°$ and $-80°$ instantly gave good yields of the trialkyl borates and pyridine hydrochloride, but little pyridine–boron trichloride. Borate formation on use of the last reagent (1 mol.), *n*-butanol (3 mols.), and pyridine (2 mols.) was much slower even at $+80°$. Addition of pyridine (1 mol.) to *n*-butyl dichloroboronite (1 mol.) gave a complex, $C_5H_5N,B(OR)Cl_2$, of similar stability to that of the ester itself. This type of complex was also formed by the interaction of alcohols (*n*- and *tert.*-butanol, octan-1-ol, octan-2-ol, and 1-phenylethanol) (1 mol.) with pyridine–boron trichloride (1 mol.) and decomposed to the trialkyl borates and on stronger heating to alkyl chlorides and pyridine–boron oxychloride. Possible mechanisms are discussed.

Addition of a non-metal halide to alcohols in the presence of pyridine has become one of the most valuable methods for the preparation of ortho-esters of these non-metals [$MX_n + n\text{ROH} + nC_5H_5N \longrightarrow M(OR)_n + nC_5H_5N,HX$]. The mechanism of the reactions, and in particular the function of the pyridine, has given rise to much speculation. The more important of these suggestions are now considered for the case where the halide is boron trichloride.

Gerrard suggested (*J.*, 1939, 99; 1940, 218) that the pyridine is combined with alcohol (ROH) by virtue of hydrogen bonding, affording the compound ROH,NC_5H_5, and it is this which in turn reacts with the non-metal halide. Reactions with boron trichloride give evidence for this view. It has been shown that reactions (1) (Gerrard and Lappert, *J.*, 1951, 1020, 2545) and (2) (*ibid.*, p. 1020; *Chem. and Ind.*, 1952, 53) are very rapid. The addition of boron trichloride to an equimolecular mixture of an alcohol and pyridine involves competition between reactions (1) and (2) but, contrary to the expectation that



the stronger base, pyridine, would dominate the situation, almost no pyridine–boron trichloride was isolated. The main products of the reaction were the trialkyl borate and pyridine hydrochloride in nearly quantitative yields, particularly when such a solvent was used as to afford the maximum homogeneity on mixing (see Table 1). The almost complete absence of (2) indicates that on addition of boron trichloride to the alcohol–pyridine mixture, the lone pair on the nitrogen atom is no longer available for reaction, such as would be the case if an ROH,NC_5H_5 complex were formed, whereas the oxygen lone-pair is still available for reaction. This is also in agreement with Cleverdon and Smith's dipole-moment work (*Chem. and Ind.*, 1948, 29).

It might be suggested that the first step in the interaction of boron trichloride with alcohols in the presence of pyridine is the formation of a complex intermediate between the trichloride and the base, *i.e.*, C_5H_5N,BCl_3, and that this then reacts with the alcohol to give the borate. Such a theory was put forward for the phosphorus pentachloride system (Hückel and Pietrzok, *Annalen*, 1939, **540**, 250) and the phosphorus oxychloride system (Boyd and Ladhams, *J.*, 1928, 215). That this view is not tenable in the boron trichloride system was demonstrated by showing that the pyridine complex (a stable white solid) reacts to a negligible extent with *n*-butanol in the presence of pyridine in chloroform at 25°, and only slowly at 80° (see Table 3) and thus the complex can play no

significant part under normal reaction times (30 min.) and temperatures (−10° or −80°) in the main reaction.

Finally, a view that requires consideration is that the pyridine may facilitate the decomposition of a chloro-ester formed as an intermediate. This was suggested for certain thionyl chloride reactions (Kenyon, Phillips, and Taylor, *J.*, 1931, 382), particularly those which produced alkyl halide. In the boron trichloride system, however, a very different situation exists because the boron atom in an alkyl dichloroboronite has an outer shell of only six electrons and this, together with the dissymmetry of the molecule, makes for considerable instability (Gerrard and Lappert, *loc. cit.*). The addition of pyridine (1 mol.) to *n*-butyl dichloroboronite (1 mol.) afforded a co-ordination complex, the stability of which was no less than that of the chloro-ester itself.

Reactions with Pyridine–Boron Trichloride.—In an earlier paper (Gerrard and Lappert, *Chem. and Ind.*, 1952, 53) reactions of pyridine–boron trichloride with alcohols in the presence of pyridine were described. Further experiments have now been carried out on the reactions in the absence of pyridine, and the alcohols studied were *n*- and *tert.*-butanol, octan-1-ol, octan-2-ol, and 1-phenylethanol. The reagents were used in equimolecular proportions and chloroform was the solvent. There was no evolution of hydrogen chloride at 20°, but at reflux temperature the gas was steadily evolved during about 20 hours. The other products depended on the individual alcohol and the time of heating. With *n*-butyl alcohol after 20 hours the trialkyl borate (33%), pyridine–boron trichloride (37·5%), and *n*-butyl dichloroboronite–pyridine (68%) were obtained. The yields refer to reactions (3) and (4). With (+)-1-phenylethanol, on the other hand, after 30 hours (±)-1-chloro-1-phenylethane (81%) and a solid which was apparently pyridine–boron oxychloride (100%) (5) were obtained.

$$ROH + C_5H_5N,BCl_3 \longrightarrow C_5H_5N,BCl_2(OR) + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

$$3C_5H_5N,BCl_2(OR) \longrightarrow B(OR)_3 + 2C_5H_5N,BCl_3 + C_5H_5N \quad . \quad . \quad . \quad . \quad (4)$$

$$ROH + C_5H_5N,BCl_3 \longrightarrow C_5H_5N,BOCl + RCl + HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The existence of boron oxychloride is considered doubtful (Martin, *Chem. Reviews*, 1944, **34**, 461). No inference may be made regarding the loss of optical activity of the alkyl halide, as (±)-1-chloro-1-phenylethane was itself racemised when heated at reflux temperature in chloroform for 7 hours. *tert.*-Butyl alcohol gave results analogous to those with 1-phenylethanol, and the two octyl alcohols gave results intermediate between these and *n*-butyl alcohol. 20 Hours' heating of (±)-octan-2-ol afforded (+)-tri-2-octyl borate (41%) and the (−)-halide (41%), whereas 60 hours' heating gave (−)-2-chloro-octane and no borate. Octan-1-ol after 60 hours afforded a mixture of the borate (87%) and the halide (8%).

These results indicated that the products of reaction (4) on prolonged heating would afford alkyl halide (RCl) and the pyridine–oxychloride complex: $(RO)_3B + 2C_5H_5N,BCl_3 + C_5H_5N \longrightarrow 3RCl + 3C_5H_5N,BOCl$. This was confirmed for tri-*n*-butyl borate by 45 hours' heating at 150°, *n*-butyl chloride (81%) being collected. A similar experiment using (+)-tri-2-octyl borate yielded the (−)-halide, with some racemisation, and a considerable elimination reaction proceeded simultaneously yielding octene.

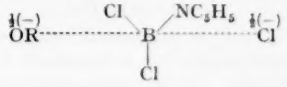
The identity of the *n*-butyl dichloroboronite–pyridine complex (3) was confirmed independently by the addition of pyridine (1 mol.) to the dichloroboronite (1 mol.). It was an oil, and on heating underwent reaction (4); on stronger heating the products reacted further as above. A complex of similar type, *viz.*, the trimethylamine complex of methyl dichloroboronite, from which trimethyl borate could be obtained, was reported by Wiberg and Sütterlin (*Z. anorg. Chem.*, 1935, **222**, 92).

Reactions with pyridine–boron trichloride may now be compared with those of the trichloride itself, and of these, four are now available for such comparison: the hydrolysis, the alcoholysis (1 mol. : 1 mol.), the reaction between trialkyl borates and the chlorinating agent, and the decomposition of chloro-esters. Whereas reactions with boron trichloride are characterised by their great velocity and completeness even at very low temperatures (*e.g.*, −80°), the opposite is the case with the pyridine complex, for prolonged heating is invariably required. The high reactivity of the former reagent is attributed to the " free

space " on the boron atom; this is no longer available in the pyridine complex. It is suggested that the first three reactions cited (*i.e.*, replacement of Cl by OH or OR, respectively, and of OR by Cl), which are essentially substitution reactions on the boron atom, are of a nucleophilic type, and a high rate of reaction will be favoured by a low electron density on the boron atom. The replacement of chlorine by hydroxyl or alkoxyl in boron trichloride may be three-centre " end-on " (1) or four-centre " broadside " (6) reactions:

$$\xrightarrow{\text{etc.}} \quad B(OR)_3 + 3HCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

The mechanism of such a replacement on pyridine–boron trichloride is considered also to be of nucleophilic type, and in view of the completed octet on the boron is pictured as completely analogous to the substitution on an aliphatic carbon atom (Hughes and Ingold; see, *e.g.*, Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603). Thus there are two possibilities, a mechanism analogous to S_N2, involving the transition state (7) or an S_N1 pre-ionisation of the complex (8), and of these the former is preferred, particularly as the complex is insoluble in water. However, the reaction is slow as the somewhat negatively charged boron has a resistance to nucleophilic attack.



$$C_5H_5N,BCl_3 \longrightarrow C_5H_5N,\overset{+}{B}Cl_2 + \overset{-}{Cl}$$

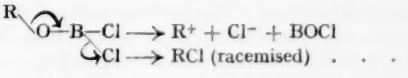
$$C_5H_5N,\overset{+}{B}Cl_2 + ROH \longrightarrow C_5H_5N,BCl_2(OR) + \overset{+}{H} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

An alternative explanation of the difference in reactivities between boron trichloride and chloro-esters compared with their pyridine complexes can be deduced from the work of Greenwood, Martin, and Emeléus (*J.*, 1950, 3030; 1951, 1328, 1795, 1915), who showed the ability of boron trifluoride to ionise a neutral oxygen-containing molecule (*e.g.*, water or diethyl ether) to form a complex anion with the negative oxygen fragment [*e.g.*, $C_2H_5^+(BF_3{\cdot}OC_2H_5)^-$; $H^+(BF_3{\cdot}OH)^-$]. If it is assumed that boron trichloride behaves likewise, then transition states in hydrolysis and alcoholysis are $H^+(BCl_3{\cdot}OH)^-$ and $H^+(BCl_3{\cdot}OR)^-$. On the other hand, anions of this type could not be formed in the case of the pyridine complexes for they would each possess a quinquevalent boron atom.

The decomposition of the chloro-esters $RO{\cdot}BCl_2$, and $C_5H_5N,B(OR)Cl_2$ presents a different problem as the products of the two reactions are of different types (4 and 9).

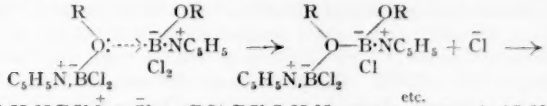
$$3RO{\cdot}BCl_2 \longrightarrow 3RCl + B_2O_3 + BCl_3 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Whatever the mechanism of (9), it is probably of the S_N1 type, as the alkyl chloride in the case of (+)-2-octyl dichloroboronite was obtained racemised (Gerrard and Lappert, *loc. cit.*), and may be as shown in (10). This suggestion requires electron-release from the alkyl



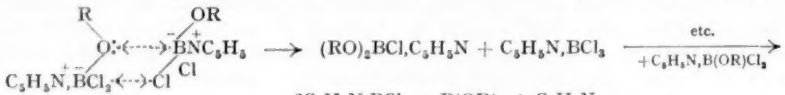
$$\overset{\curvearrowright}{Cl} \longrightarrow RCl \text{ (racemised)} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

group owing to a somewhat positive oxygen atom, and it has been shown that the stability of dichloroboronites is lower the greater the electron-release of the alkyl group. The corresponding pyridine complexes would not have the same tendency, for the electron density on the oxygen atom is not deficient, the boron atom being negatively charged, but

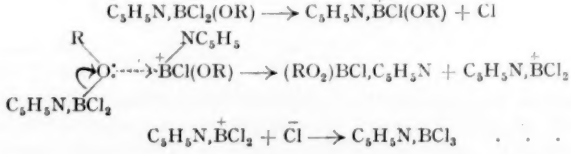


$$[C_5H_5N,BCl_2]^+ + \overset{-}{Cl} + (RO)_2BCl,C_5H_5N \xrightarrow[+C_5H_5N,B(OR)Cl_2]{\text{etc.}} 2C_5H_5N,BCl_3 + B(OR)_3 + C_5H_5N \quad . \quad (11)$$

more likely uses a mechanism analogous to (7) [see (11) or (12)], the borate being obtained with retained configuration. A more likely mechanism may be the S_N1 type (13).



$$2C_5H_5N,BCl_3 + B(OR)_3 + C_5H_5N \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$



$$C_5H_5N,BCl_3 + \bar{C}l \longrightarrow C_5H_5N,BCl_4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

When the pyridine complex was heated more strongly, alkyl chloride was obtained: $C_5H_5N,B(OR)Cl_2 \longrightarrow RCl + C_5H_5N,BOCl$; and here it was completely inverted. This may be due to S_N1 pre-ionisation of the complex, or of pyridine–boron trichloride, chlorine anion then attacking by S_N2 " end-on " mechanism on the carbon atom.

Experimental

Addition of Boron Trichloride (1 *mol.*) *to Alcohols* (3 *mols.*) *in Presence of Pyridine* (3 *mols.*).—The results obtained in these experiments are summarised in Tables 1 and 2, and only the general technique need be described. Boron trichloride (1 mol.) in solvent (15% solution) was slowly (30—60 min.) added to a mixture of the alcohol (0·05—0·10 molar scale, 3 mols.) and pyridine (3 mols.) in solvent (50%), which was cooled to −10° or −80°. In the experiments using *n*-pentane, a mixture of pyridine hydrochloride and pyridine–boron trichloride was precipitated instantly, whereas in chloroform no precipitate formed for both these solids are readily soluble therein. The mixtures were kept for 3 hours at 15—20°. In the chloroform experiments, the solvent was removed at room temperature at 15 mm. and *n*-pentane was added. Both series of experiments were then treated identically. The precipitate was quantitatively filtered off, washed with pentane, placed in a vacuum-desiccator, and weighed. It was then washed with water, and the residue was returned to the desiccator. The water-insoluble solid was pyridine–boron trichloride and the filtrate contained the pyridine hydrochloride. The pentane was removed from the primary filtrate in a vacuum, and the residue (after filtration of the slight precipitate of pyridine hydrochloride which formed on removal of the solvent) was distilled. A small fore-run of unchanged alcohol and pyridine was first obtained, and then the trialkyl borate distilled. In the experiments with *tert.*-butyl alcohol the purification of the trialkyl borate was particularly difficult; hence the crude yields are given in Table 1. To obtain pure specimens two or three further fractionations were required, which lowered the yield to 38% at the best.

Interaction of Alcohols (1 *mol.*) *and Pyridine–Boron Trichloride* (1 *mol.*).—*Octan*-1-*ol*. The alcohol (1·23 g., 1 mol.) and pyridine–boron trichloride (Gerrard and Lappert, *loc. cit.*) (1·90 g., 1 mol.) were refluxed in chloroform (10 c.c.) for 7 days. Hydrogen chloride was continuously evolved. The chloroform was distilled and a pasty white residue remained. This was extracted with successive portions of *n*-pentane. The pentane extract afforded 1-chloro-octane (0·15 g., 8%), b. p. 60—70°/13 mm., n_D^{16} 1·4335, and tri-1-octyl borate (1·10 g., 87%), b. p. 175°/0·5 mm., n_D^{16} 1·4378 (Found: B, 2·8. Calc. for $C_{24}H_{51}O_3B$: B, 2·72%). The pentane-insoluble matter was pasty and was soluble in water.

n-*Butyl alcohol*. The alcohol (3·75 g., 1 mol.) and pyridine–boron trichloride (10·0 g., 1 mol.) in chloroform (15 c.c.) had afforded no hydrogen chloride after 15 hours at 20°. In these experiments effluent hydrogen chloride was absorbed in potassium hydroxide. At reflux temperature the gas (1·66 g., 72%) was evolved in 9 hours, and a further 0·23 g. (10%) was collected after another 11 hours. No boron trichloride was liberated. The mixture on distillation afforded chloroform (12 c.c.), b. p. 62—65°, and a pasty residue which was leached with *n*-pentane, and thereby yielded tri-*n*-butyl borate (1·3 g., 33%), b. p. 105°/8 mm., n_D^{17} 1·4112 (Found: B, 4·83. Calc. for $C_{12}H_{27}O_3B$: B, 4·72%). The remaining solid was washed with water and left pyridine–boron trichloride (2·50 g., 37·5%), m. p. 114°. The aqueous filtrate contained pyridine (2·61 g.), chloride ion (2·24 g.), and boron (0·351 g.). These products were

evidently formed by the hydrolysis of *pyridine–n-butyl dichloroboronite* (7·5 g., 68%). The latter on hydrolysis would give pyridine (2·54 g.), chloride ion (2·28 g.), and boron (0·349 g.) (as boric acid).

TABLE 1.

R in ROH	Yields, %, in pentane At −80° $B(OR)_3$	C_5H_5N, HCl	C_5H_5N, BCl_3	Yields, %, in pentane At −10° $B(OR)_3$	C_5H_5N, HCl	C_5H_5N, BCl_3	Yields, %, in chloroform At −10° $B(OR)_3$	C_5H_5N, HCl	C_5H_5N, BCl_3
Bu^n	76	89·5	10·5	74	87	12·9	88	91	9·1
Bu^i	69	80·1	19·9	72	81	19·2	93	99	1·0
Bu^s	65	75·6	24·3	70	92·8	7·0	92	96	4·1
Bu^t	50 *	74	26·2	69 *	92·5	7·4	71 *	98	1·8
1-Octyl ...	—	—	—	77	84	16	90	98	2·8
2-Octyl †	—	—	—	64	79·5	20·5	84	91·8	8·2
CHPhMe †	—	—	—	69 (RCl, 21%)	—	—	86	93	7·0

* Crude yield. † Gerrard and Lappert (*loc. cit.*).

1-*Phenylethanol*. The alcohol (5·1 g., 1 mol.; α_D^{20} +24·1°) and pyridine–boron trichloride (8·22 g., 1 mol.) were mixed with chloroform (25 c.c.) at 20°. No heat was developed on mixing nor was any hydrogen chloride evolved. After the mixture had been refluxing for 10 hours, 1·17 g. of hydrogen chloride had been evolved; and further quantities of 0·380 g. and 0·0285 g. had been evolved after two further periods of 10 hours each (*i.e.*, total HCl, 1·58 g. Calc.: 1·55 g.). The chloroform was removed in a vacuum; a pasty solid remained, which was extracted with four successive portions (15 c.c. each) of *n*-pentane. The pentane extract on distillation gave (±)-1-chloro-1-phenylethane (4·90 g., 81%), b. p. 80°/15 mm., n_D^{19} 1·5284, α_D^{20} 0° (Found: Cl, 24·9. Calc. for C_8H_9Cl: Cl, 25·3%). The residue (6·07 g.) after pentane extraction was a pasty solid, which appeared to be *pyridine–boron oxychloride* (Calc.: 5·92 g.) (Found: Cl, 25·3; B, 7·4; C_5H_5N, 54·1. C_5H_5ONClB requires Cl, 25·1; B, 7·65; C_5H_5N, 55·8%). It was readily hydrolysed by water. (Yields in this experiment are based on: $ROH + C_5H_5N,BCl_3 \longrightarrow C_5H_5N,BOCl + RCl + HCl$.) (+)-1-Chloro-1-phenylethane (1·97 g., α_D^{20} +34·2°) was heated in chloroform (10 c.c.) for 7 hours at reflux temperature. The solvent was removed in a vacuum and (±)-1-chloro-1-phenylethane (1·83 g., α_D^{20} 0°), b. p. 92°/33 mm., n_D^{23} 1·5302 (Found: Cl, 25·2%), was recovered.

TABLE 2.

R in ROH	In pentane At −80° B. p./mm.	n_D^t	At −10° B. p./mm.	n_D^t	In chloroform At −10° B. p./mm.	n_D^t
Bu^n	109°/15	(20°) 1·4108	116—118°/20	(18°) 1·4106	113°/15	(18°) 1·4106
Bu^i	84—86/10	(20) 1·4035	90/14	(20) 1·4037	90/14	(20) 1·4035
Bu^s	79—80/11	(20) 1·3968	81/15	(17) 1·3980	82/15	(17) 1·3989
Bu^t	64/14	(20) 1·3880	66/17	(21) 1·3881	65/16	(20) 1·3885
1-Octyl ...	—	—	174/0·4	(16) 1·4385	173/0·4	(16) 1·4385

The boron analyses of the various borate samples and the chloride analyses of the pyridine hydrochloride specimens obtained from each reaction were all within 1% of the calculated values.

Octan-2-ol. The (+)-alcohol (6·5 g., 1 mol.; α_D^{20} +4·3°) and pyridine–boron trichloride (9·83 g., 1 mol.) were dissolved in chloroform (25 c.c.). No hydrogen chloride was evolved after 3 days at 20°, but during 20 hours at reflux temperature the gas (1·89 g. Calc.: 1·85 g.) was evolved. The solvent was removed in a vacuum and the residue was extracted with *n*-pentane. This extract afforded (−)-2-chloro-octane (3·10 g., 41%), b. p. 69°/18 mm., α_D^{20} −14·6°, n_D^{20} 1·4279°, and (+)-tri-2-octyl borate (2·73 g., 41%), b. p. 140°/0·1 mm., α_D^{20} +16·6°, $n_D^{16.5}$ 1·4292° (Found: B, 2·82. Calc. for $C_{24}H_{51}O_3B$: B, 2·72%). Water was added to the pentane-insoluble pasty solid and the mixture was filtered. The residue was pyridine–boron trichloride (1·61 g., 16·4%), m. p. 114°, and the water-soluble portion was probably a mixture of pyridine-2-octyl dichloroboronite and pyridine–boron oxychloride (Found: C_5H_5N, 2·94 g.; Cl, 1·26 g.; B, 0·226 g.). In a duplicate experiment (+)-octan-2-ol (5·96 g., 1 mol.; α_D^{20} +4·3°) and pyridine–boron trichloride (9·0 g., 1 mol.) were heated in chloroform (13 c.c.) at reflux temperature for 70 hours. Hydrogen chloride (1·70 g., 99%) was evolved. Pentane extraction of the chloroform-free residue yielded (−)-2-chloro-octane (5·31 g., 78%), b. p. 63°/16 mm., α_D^{20} −14·5°, n_D^{20} 1·4280 (Found: Cl, 23·4. Calc. for $C_8H_{17}Cl$: Cl, 23·9%). The pentane-

insoluble residue contained pyridine–boron trichloride (0·148 g., 1·7%) and apparently crude pyridine–boron oxychloride (Found: C_5H_5N, 3·56 g.; Cl, 1·65 g.; B, 0·497 g. Calc.: total C_5H_5N 3·66 g.; $\frac{1}{3}$Cl, 1·65 g.; B, 0·502 g. in system).

tert.-*Butyl alcohol.* The alcohol (2·12 g., 1 mol.) and pyridine–boron trichloride (5·62 g., 1 mol.) in chloroform (10 c.c.) were heated for 30 hours under reflux. Evacuation (15 mm.) left a pasty white solid (4·94 g. Calc. for $C_5H_5N,BOCl$: 5·10 g.), which appeared to be pyridine–boron oxychloride (Found: Cl, 24·7; B, 7·4; C_5H_5N, 55·4%). Pure *tert.*-butyl chloride could not be isolated from the condensate owing to difficulty of fractionation.

Interaction of Trialkyl Borates (1 *mol.*), *Pyridine–Boron Trichloride* (2 *mols.*), *and Pyridine* (1 *mol.*).—*Tri*-n-*butyl borate.* The borate (2·84 g., 1 mol.), pyridine–boron trichloride (4·84 g., 2 mols.), and pyridine (0·971 g., 1 mol.) were heated at 150° in absence of solvent for 45 hours under reflux. On evacuation (15 mm.) of the reaction vessel, *n*-butyl chloride (2·84 g., 81%), b. p. 78—79°, n_D^{20} 1·4028 (Found: Cl, 38·2. Calc. for C_4H_9Cl: Cl, 38·4%), was condensed in a trap at −80° and a hard black residue remained in the flask. Carbonaceous decomposition of this solid took place at 200°/0·05 mm., pyridine being collected in the " Drikold " trap.

Tri-2-*octyl borate.* The (+)-borate (3·87 g., 1 mol.; α_D^{20} +16·5°; from ROH, α_D^{20} +4·3°), pyridine–boron trichloride (3·73 g., 2 mols.), and pyridine (0·750 g.) were heated in absence of solvent at 150° for 45 hours. Distillation afforded a mixture (3·80 g.) (Found: Cl, 5·5%) of octene (77%) and (−)-2-chloro-octane which on bromination and distillation gave (−)-2-chloro-octane (0·81 g.), b. p. 88°/40 mm., n_D^{20} 1·4284, α_D^{20} −6·8° (Found: Cl, 23·6%), and dibromo-octene (1·70 g.), b. p. 135—140°/30 mm., n_D^{20} 1·4970. The residue (4·36 g.) from the primary distillation was hard and black, owing probably to some decomposition. It was largely soluble in water and contained pyridine (2·22 g.), chloride ion (1·44 g.), and boron (0·266 g.) (as boric acid).

Approximate Rate of Reaction of Pyridine–Boron Trichloride (1 *mol.*), *Pyridine* (2 *mols.*), *and* n-*Butanol* (3 *mols.*).—The results of these experiments are summarised in Table 3. From a

TABLE 3.

Time (hr.)	Temp.	Reaction, %: * (based on weight of C_5H_5N,BCl_3)	(based on weight of C_5H_5N,HCl)	Found: Cl, % (Calc. for C_5H_5N,HCl: Cl, 30·7%)
3	25°	4·1	3·1	30·4
48	25	5·4	5·0	30·5
336	25	9·2	8·7	30·5
0·5	80	27·2	25·7	30·6
1	80	40·0	38·2	30·6
2	80	60·1	58·4	30·3
3	80	73·4	73·6	30·2
4	80	81·4	79·3	30·6

* Based on $C_5H_5N,BCl_3 + 2C_5H_5N + 3C_4H_9{\cdot}OH \longrightarrow B(OC_4H_9)_3 + 3C_5H_5N,HCl$.

solution containing pyridine–boron trichloride (7·50 g., 1 mol.), pyridine (6·03 g., 2 mols.), and *n*-butanol (8·47 g., 3 mols.) in chloroform (100 c.c.) kept at either 25° or 80°, samples (10 c.c.) were withdrawn at arbitrary intervals. The chloroform was rapidly removed at 25°/0·2 mm., and *n*-pentane was added to the residue. The precipitate of pyridine–boron trichloride together with pyridine hydrochloride was filtered off, placed in a vacuum-desiccator, and weighed; it was then washed with water; only the water-insoluble pyridine–boron trichloride remained and this was returned to the desiccator. A chloride estimation was carried out on the aqueous washings.

Interaction of Pyridine (1 *mol.*) *and* n-*Butyl Dichloroboronite* (1 *mol.*).—Pyridine (2·18 g., 1 mol.) in *n*-pentane (15 c.c.) was added to *n*-butyl dichloroboronite (Gerrard and Lappert, *loc. cit.*) (4·27 g., 1 mol.) also in *n*-pentane (15 c.c.) at −80°. A white precipitate was formed immediately and changed to a yellow oil, immiscible with and denser than pentane, when the mixture was allowed to warm to 20° (30 min.). The oil was separated from the solvent and filtered from a slight remaining precipitate. On evacuation (20 mm.) the oil (5·89 g., 91%) remained and was apparently *pyridine–*n-*butyl dichloroboronite* (Found: Cl, 30·5; C_5H_5N, 34·2; B, 4·7. $C_9H_{14}ONCl_2B$ requires Cl, 30·4; C_5H_5N, 33·8; B, 4·62%), which was readily decomposed by water to pyridine, hydrogen chloride, and boric acid.

*Action of Heat on Pyridine–*n-*Butyl Dichloroboronite.*—A sample of the complex (5·00 g.) was heated at 100° for 1 hour. Water was added and the water-insoluble pyridine–boron trichloride (0·660 g., 13·2%) was filtered off. [Yield is based on: $3C_5H_5N,Cl_2BOR \longrightarrow$

$B(OR)_3 + 2C_5H_5N,BCl_3 + C_5H_5N$.] In a separate experiment distillation of the complex (4·90 g.) was attempted and the distillate consisted of two layers; the upper on filtration and distillation afforded tri-*n*-butyl borate (1·4 g., 97%), b. p. 64°/0·5 mm., n_D^{14} 1·4125 (Found: B, 4·9. Calc. for $C_{12}H_{27}O_3B$: B, 4·7%), and the lower gave pyridine–boron trichloride (2·0 g., 80%), b. p. 170°/0·4 mm., m. p. 114°.

When the complex (8·02 g.) was heated at 150° for 45 hours under reflux, and the mixture cooled, a hard black solid separated, covered by a supernatant clear liquid, which on being decanted and distilled afforded *n*-butyl chloride (2·70 g., 84%), b. p. 78—79°, n_D^{14} 1·4007 (Found: Cl, 38·0. Calc. for C_4H_9Cl: Cl, 38·4%). The black solid (5·02 g. Calc. for $C_5H_5N,BOCl$: 4·84 g.) was completely water-soluble, except for a slight black tar, and appeared to be crude pyridine–boron oxychloride (Found: C_5H_5N, 53·2; Cl, 26·7; B, 7·6%).

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136. *Peptides. Part IV.* Selective Removal of the C-Terminal Residue as a Thiohydantoin. The Use of Diphenyl Phosphorisothiocyanatidate.†*

By G. W. KENNER, H. G. KHORANA, and R. J. STEDMAN.

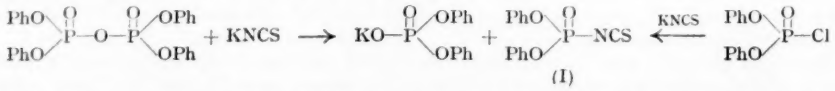
Diphenyl phosphoro*iso*thiocyanatidate (I) is conveniently prepared from diphenyl phosphorochloridate and potassium thiocyanate. In acetonitrile or dimethylformamide solution, with the triethylamine salts of *N*-acylated peptides it gives 1-acyl-2-thiohydantoins (V) in high yield. As shown already by others, these substances are readily hydrolysed by alkali to a thiohydantoin (VI) and the acylated peptide or amino-acid lacking the terminal residue.

PART III of this series * described a method for selective removal from a peptide chain of the amino-acid bearing a free carboxyl group, the "*C*-terminal residue" (Sanger, *Adv. Protein Chem.*, 1952, **7**, 1). This procedure appears superior to older ones; yet it is not wholly satisfactory, for the degraded peptide derivative is sometimes seriously contaminated with the starting material. Of the earlier methods the most promising is that of Schlack and Kumpf (*Z. physiol. Chem.*, 1926, **154**, 125), which involves conversion of an *N*-acylpeptide into an acylthiohydantoin (V) and subsequent alkaline cleavage of this intermediate to (VI) and (VII). A recent study of this method (Waley and Watson, *J.*, 1951, 2394) confirms its general soundness and suggests that the principal difficulty lies in the first step, treatment of the original *N*-acylpeptide with acetic anhydride and ammonium thiocyanate at 100°. We now describe an alternative technique, which gives high yields of acylthiohydantoins (V) under mild conditions and therefore adds considerably to the value of Schlack and Kumpf's method.

The preparation of acylthiohydantoins by means of acetic anhydride and ammonium thiocyanate is due to T. B. Johnson and his collaborators (*J. Amer. Chem. Soc.*, 1913, **35**, 1130, 1136; and earlier papers), who considered that the function of these reagents was to produce a mixed anhydride, an acyl *iso*thiocyanate (IV), which would then isomerise to the acylthiohydantoin. Corby, Kenner, and Todd (*J.*, 1952, 1234) recently showed that mixed anhydrides are frequently accessible through "exchange reactions" between anhydrides and anions, owing to the tendency for production of the least reactive anhydride by elimination of the stable ion corresponding to the strongest acid. Thiocyanic acid is relatively strong in aqueous solution (Suzuki and Hagisawa, *Chem. Abs.*, 1949, **43**, 2074; Gorman and Connell, *J. Amer. Chem. Soc.*, 1947, **69**, 2063) but significantly weaker in alcohol (Murray-Rust and Hartley, *Proc. Roy. Soc.*, 1930, *A*, **126**, 84). We therefore expected its anion to enter into exchange reactions. Tetraphenyl pyrophosphate proved to be an anhydride sufficiently reactive to undergo exchange with potassium thiocyanate,

* Part III, *J.*, 1952, 2081. † For nomenclature see *Proc.*, 1952, 138.

for a mixture of their acetonitrile solutions rapidly deposited potassium diphenyl phosphate, leaving diphenyl phospho*iso*thiocyanatidate (I) in solution. This new mixed anhydride

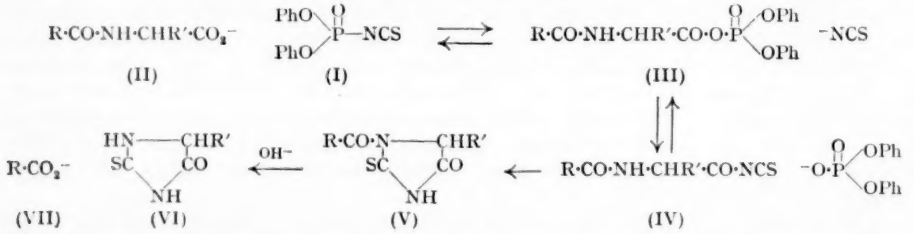


(I)

is obtained more directly from diphenyl phosphorochloridate (chlorophosphonate) and potassium thiocyanate. Its structure is confirmed by comparison of its refractivity (75·83) with that of diphenyl phosphorochloridate (66·07); the difference between these values (9·76) agrees well with that expected from Vogel's results (*J.*, 1948, 1842) for the *iso*thiocyanato-structure (9·77) but not with that corresponding to the thiocyanato-structure (7·56). Still stronger evidence is afforded by the addition of *cyclo*hexylamine to give *N*-diphenoxyphosphinyl-*N'-cyclo*hexylthiourea, $C_6H_{11}\cdot NH\cdot CS\cdot NH\cdot PO(OPh)_2$. This reaction is analogous to the behaviour of acyl *iso*thiocyanates, for instance, benzoyl *iso*thiocyanate (Dixon and Taylor, *J.*, 1908, **93**, 684), but, in contrast to these cases, none of the simple amide, diphenyl phosphoramidate, is obtained by hydrolysis with dilute acid or alkali. This circumstance is fortunate for the application of (I) to the preparation of neutral substances, in particular acylthiohydantoins.

When the mixed anhydride (I) is brought into contact with the triethylammonium salt of an *N*-acylpeptide, further exchange reactions take place. The anion (II) of this relatively weak oxyacid can displace the *iso*thiocyanate ion, forming an acyl phosphate (III), which in turn is attacked by the *iso*thiocyanate ion giving the desired acyl *iso*thiocyanate (IV). The net effect is total elimination of the diphenyl phosphate anion. As the subsequent isomerisation of the acyl *iso*thiocyanate (IV) into the acylthiohydantoin (V) is effectively irreversible the whole process proceeds to completion.

5-Benzyl-2-thio-1-toluene-*p*-sulphonylglycylhydantoin (V; $R = C_6H_4Me\cdot SO_2\cdot NH\cdot CH_2$, $R' = CH_2Ph$) is obtained from the triethylamine salt of toluene-*p*-sulphonylglycyl-DL-phenylalanine in quantitative yield in 110 hours (after 14 and 24 hours, 55 and 84% respectively). The slowness of the process contrasts with the rapidity of exchange between tetraphenyl pyrophosphate and the anions of dibenzyl phosphate (Mason and Todd, *J.*, 1951, 2267) and thiocyanic acid (see above), but is not surprising in view of the number of possible side equilibria. The alternative, less convenient, technique



(II) (I) (III) (VII) (VI) (V) (IV)

of adding tetraphenyl pyrophosphate to a mixture of potassium thiocyanate and the triethylammonium salt in acetonitrile appears to permit a rather faster reaction; the thiohydantoin (V; $R = C_6H_4Me\cdot SO_2\cdot NH\cdot CH_2$, $R' = CH_2Ph$) is obtained in 96% yield after only 24 hours. By the former method a number of simple acylthiohydantoins were prepared without difficulty, except that in the cases with a terminal glycine residue (*i.e.*, R' = H) the solution became coloured, presumably owing to minor condensation reactions of the reactive methylene group in (V; R' = H).

Waley and Watson (*J.*, 1951, 2394) showed that 1-carbobenzyloxyglycyl-5-methyl-2-thiohydantoin is hydrolysed by 0·1N-sodium hydroxide at 0° in 20 minutes. In testing the generality of this cleavage we found it convenient to follow the reaction spectroscopically, essentially according to the procedure of Kjaer and Eriksen (*Acta Chem. Scand.*, 1952, **6**, 448). As hydrolysis with 0·01N-alkali at room temperature proceeds, the ratio between the optical densities at 262 and 278 mμ of samples, withdrawn and diluted with

acid, increases. It does not, however, reach the expected constant figure, and falls gradually again after rapidly reaching a maximum. The plausible explanation, that the thiohydantoin ring in both (V) and (VI) is attacked by alkali, is supported by the observation that the ultra-violet absorption of 5-*iso*butyl-2-thiohydantoin at 260 mμ diminishes gradually in 0·01N-alkali. It is therefore not surprising that, in our experience, hydrolysis by two equivalents of 0·01N-sodium hydroxide during 30 minutes at room temperature gives satisfactory, but by no means quantitative, yields of the desired products. In the case of (V; R = $C_6H_4Me{\cdot}SO_2{\cdot}NH{\cdot}CH_2$, R′ = CH_2Ph) the reaction is unusually slow, doubtless owing to the influence of the ionised sulphonamide group, but the hydrolysis products are obtained in good yield.

Sheehan and Frank (*J. Amer. Chem. Soc.*, 1950, **72**, 1312) have demonstrated the ready synthesis of the peptide linkage through anhydrides of the type (III), which are unfortunately not readily accessible. It seemed possible that the exchange reaction between a tetraester of pyrophosphoric acid and the anion of an *N*-acylpeptide or amino-acid might provide a convenient method of their preparation. But experiments on the condensation of toluene-*p*-sulphonylalanine with *cyclo*hexylamine were unpromising, whether the pyrophosphate applied was tetrabenzyl, tetraphenyl, or tetra-*p*-nitrophenyl (Khorana and Todd, unpublished work). Presumably in the basic reaction medium the acyl phosphates (III) are rapidly brought into equilibrium with the two symmetrical anhydrides, a reaction observed by Sheehan and Frank (*loc. cit.*). This equilibrium is unimportant in the preparation of acylthiohydantoins owing to the irreversibility of the final cyclisation step.

Experimental

M.p.s are corrected.

Diphenyl Phosphoroisothiocyanatidate (I).—(a) *From diphenyl phosphorochloridate.* Diphenyl phosphorochloridate (chlorophosphonate) (Brigl and Müller, *Ber.*, 1939, **72**, 2121) had n_D^{20} 1·5502. From d_4^{20} 1·2960 (Anschütz and Emery, *Annalen*, 1889, **253**, 120), $[R_L]_D$ is 66·07. The addition of this substance (50·1 g.) to a solution of potassium thiocyanate (19·3 g.) in acetonitrile (200 c.c.) caused immediate deposition of a white solid, accompanied by a slight rise in temperature. The mixture was shaken during 3 hours, kept for 3 hours more, and diluted with dry benzene (300 c.c.). The solid was removed and the filtrate evaporated in a vacuum to a clear yellow liquid which, purified by short-path distillation at 105°/0·1 mm., had n_D^{20} 1·5829 (43·5 g.). This *ester* was used in further work, but a portion purified by fractionation [b. p. 210°(bath)/0·1 mm.] had n_D^{20} 1·5851, d_4^{14} 1·2877, $[R_L]_D$ 75·83 (Found: C, 54·0; H, 3·5; N, 4·7. $C_{13}H_{10}O_3NPS$ requires C, 53·6; H, 3·5; N, 4·8%).

(b) *From tetraphenyl pyrophosphate.* When prepared on 0·3-mole scale according to Corby, Kenner, and Todd (*J.*, 1952, 1238) tetraphenyl pyrophosphate crystallised (m. p. 42—47°). When its acetonitrile solution (9·75 c.c. containing 4·21 mmoles) was added to a solution of potassium thiocyanate (0·408 g., 4·21 mmoles) in acetonitrile (10 c.c.), a gelatinous solid separated within a few minutes and was removed after 3 hours. Short-path distillation of the evaporated filtrate at 90°/0·05 mm. gave diphenyl phosphor*iso*thiocyanatidate as a pale yellow mobile liquid, n_D^{20} 1·5811 (Found: C, 54·3; H, 3·0; N, 5·4%).

N-*Diphenoxyphosphinyl*-N′-cyclo*hexylthiourea.*—*cyclo*Hexylamine (1·5 c.c.) was added to a solution of diphenyl phosphoro*iso*thiocyanatidate in acetonitrile (5 c.c. containing 2·38 mmoles), whereupon heat was evolved and crystals were rapidly deposited. Next day the neutral fraction was isolated from the evaporated mixture by partition, in the usual manner with thorough back-extractions, between ethyl acetate and 3N-hydrochloric acid, followed by aqueous sodium hydrogen carbonate solution and water. It consisted of a pale yellow syrup (0·956 g., 2·45 mmoles), from which the *thiourea* (0·673 g.) was obtained as colourless prisms (from aqueous ethanol), m. p. 129·5—130·5° (Found, in material dried at 70°: C, 58·6; H, 6·0; N, 7·2. $C_{19}H_{23}O_3N_2PS$ requires C, 58·4; H, 5·9; N, 7·2%).

Hydrolysis of Diphenyl Phosphoroisothiocyanatidate.—(a) *By acid.* Diphenyl phosphoro*iso*thiocyanatidate (0·338 g.) was dissolved in dioxan (20 c.c.) and N-sulphuric acid (15 c.c.). After 24 hours the solution was neutralised with aqueous sodium carbonate solution and evaporated to dryness at 50°/1 mm. Partition of the residue between ethyl acetate, aqueous sodium hydrogen carbonate solution, and water, yielded only 0·017 g. of neutral fraction.

(b) *By alkali.* A mixture of the phosphoro*iso*thiocyanatidate (0·286 g.), saturated aqueous

sodium hydrogen carbonate solution (10 c.c.), water (25 c.c.), and dioxan (25 c.c.) likewise gave only 0·018 g. of neutral fraction after 24 hours.

5-Benzyl-2-thio-1-toluene-p-sulphonylglycylhydantoin (V; R = $C_6H_4Me{\cdot}SO_2NH{\cdot}CH_2$, R′ = CH_2Ph.—(a) *By use of acetic anhydride.* Acetic anhydride (4 c.c.), acetic acid (0·5 c.c.), ammonium thiocyanate (0·5 g.) and toluene-*p*-sulphonylglycyl-DL-phenylalanine (1 g.; unpublished preparation by Mr. D. W. Clayton in this laboratory) were heated during 30 minutes at 100°. The deep red-brown solution was then poured into water (100 c.c.), treated with excess of sodium hydrogen carbonate, and extracted with ethyl acetate (4 × 50 c.c.). Evaporation of the ethyl acetate left a brown gum (1·34 g.), from which the *acylthiohydantoin* (0·26 g.; m. p. 72°) was obtained by crystallisation from benzene (150 c.c.). Recrystallisation from benzene (15 c.c.) afforded colourless plates, m. p. 72° with previous softening (Found, in material dried at 50° over paraffin wax: C, 59·0; H, 5·2; N, 8·8. Calc. for $C_{19}H_{19}O_4N_3S_2,C_6H_6$: C, 60·6; H, 5·1; N, 8·5%), whereas recrystallisation from aqueous ethanol gave colourless prisms, m. p. 166—169° (Found, in material dried at 95°: C, 54·6; H, 4·8; N, 9·9. $C_{19}H_{19}O_4N_3S_2$ requires C, 54·7; H, 4·6; N, 10·1%).

(b) *By use of diphenyl phosphoroisothiocyanatidate.* (i) Toluene-*p*-sulphonylglycyl-DL-phenylalanine (0·376 g., 1 mmole) was kept during 110 hours in acetonitrile (15 c.c.) with triethylamine (0·16 c.c., 1·16 mmole) and an acetonitrile solution of the phosphoro*iso*thiocyanatidate (2·31 c.c., containing 1·1 mmoles). The solvent was evaporated under reduced pressure and the residue separated into neutral and acidic fractions by partition between ethyl acetate (50 c.c.) and N-hydrochloric acid (30 c.c.), which was rejected after four further extractions, followed by extraction of the ethyl acetate with aqueous sodium hydrogen carbonate solution (3 × 15 c.c.) and water (2 × 15 c.c.). After back-extractions the acylthiohydantoin was recovered, by evaporation of the ethyl acetate, as a pale yellow foam (0·422 g., 1·01 mmole); crystallised from benzene (20 c.c.), it had m. p. 72—74° (0·441 g., 0·89 mmole). Thorough extraction with ethyl acetate of the acidified aqueous layers gave diphenyl hydrogen phosphate (0·279 g., 1·11 mmole) as a colourless gum crystallising slowly in rosettes.

(ii) Reaction for 24 hours gave as neutral fraction 0·350 g. (0·84 mmole) and 0·356 g. in the acid fraction (1·11 mmoles of diphenyl hydrogen phosphate and 0·19 mmole of starting material). Reaction for 14 hours gave 0·55 and 0·54 mmole, respectively.

(c) *By use of tetraphenyl pyrophosphate.* A solution of tetraphenyl pyrophosphate in acetonitrile (5·2 c.c., containing 2·25 mmoles) was added to a solution of toluene-*p*-sulphonylglycyl-DL-phenylalanine (0·752 g., 2 mmoles), triethylamine (0·275 c.c., 2 mmoles), and potassium thiocyanate (0·234 g., 2·4 mmoles) in acetonitrile (25 c.c.). After 3 hours deposition of potassium diphenyl phosphate began and this was collected after 24 hours (0·501 g., 1·74 mmoles). The dissolved material was separated in the usual way into diphenyl hydrogen phosphate (0·706 g., 2·82 mmoles) and the thiohydantoin, a pale yellow foam (0·795 g., 1·91 mmoles), m. p. 72—74° (0·955 g., 1·93 mmoles).

General Method for the Preparation of 1-Acyl-5-alkyl-2-thiohydantoins (V).—To a solution of the *N*-acylpeptide (2 mmoles) in anhydrous acetonitrile (15 c.c.) were added triethylamine (0·3 c.c., 2·2 mmoles) and then diphenyl phosphoro*iso*thiocyanatidate (0·640 g., 2·2 mmoles). The solution was kept at room temperature in a sealed flask during 2 days and then evaporated in a vacuum. The solution of the residue in ethyl acetate (25 c.c.) was twice washed with 2N-hydrochloric acid (30 c.c. total) and then mixed with water (25 c.c.). Aqueous sodium hydrogen carbonate solution was then added in small portions to the vigorously shaken mixture until the pH of the aqueous phase reached 7. The product was then recovered by evaporation of the dried ethyl acetate layer and recrystallised for analysis from acetone by addition of light petroleum (b. p. 40—60°). For results see Table 1.

Spectrophotometric Study of the Alkaline Hydrolysis of 1-Acyl-2-thiohydantoins.—As expected from published data, the absorption of 1-benzoylglycyl-5-*iso*butyl-2-thiohydantoin in 0·001N-hydrochloric acid had $\varepsilon_{max.}$ 19,530 at 278 mμ and $\varepsilon_{max.}$ 28,700 at 236 mμ, whereas that of 5-*iso*butyl-2-thiohydantoin in the same medium showed $\varepsilon_{max.}$ 17,400 at 262 mμ and $\varepsilon_{max.}$ 10,100 at 228 mμ. A solution of the latter compound in 0·01N-sodium hydroxide was kept at 18° and aliquots were removed and acidified with hydrochloric acid to 0·001N before measurement of the optical density at 262 mμ (1-cm. cuvettes, Beckman DU instrument), with results as in Table 2. The former compound (18·4 mg., 0·05 mmole) was rapidly dissolved in 0·01N-sodium hydroxide (10 c.c.). Aliquots (2 c.c.) were removed, acidified with 0·01N-hydrochloric acid (7 c.c.), diluted with aqueous alcohol (40%) to 50 c.c. and then ten times further diluted with 0·001N-hydrochloric acid for optical density measurements (Table 3). The same technique was employed for the leucyl compound (Table 4).

For the compound of Table 5 the amount of substance was reduced so that three equivalents of alkali were present. The compound had maxima at 280 (ε 15,700) and 234 mμ (ε 22,700).

Products of Alkaline Hydrolysis of 1-*Benzoylglycyl*-5-iso*butyl*-2-*thiohydantoin*.—The acylthiohydantoin (0·167 g.) was kept with 0·01N-sodium hydroxide (100 c.c., 2 equivs.) for 30 minutes. The solution was then brought to pH 6 with dilute hydrochloric acid, concentrated in a vacuum to small bulk, and thoroughly extracted with ether. Evaporation of the dried ethereal extract yielded crude 5-*iso*butyl-2-thiohydantoin (0·091 g.; theor., 0·086 g.); recrystallisation from benzene removed a little insoluble amorphous material and gave the product, m. p. 165—168° (Schlack and Kumpf record m. p. 170—171°), depressed to 152—155° on admixture with starting material. The aqueous layer was acidified with N-hydrochloric acid (1 c.c.) and evaporated to dryness in a vacuum. Hippuric acid (0·091 g.; theor., 0·090 g.) was recovered from the residue by extraction with ethyl acetate but was contaminated with brown impurities of sulphurous odour.

Products of Alkaline Hydrolysis of 1-*Benzoylglycyl*-5-iso*propyl*-2-*thiohydantoin*.—The acylthiohydantoin (0·177 g.) was dissolved (shaking) in 0·001N-sodium hydroxide (111 c.c., 2 equivs.) and kept at 20° during 15 minutes. Isolation of the neutral and the acid fraction as in the preceding experiment gave 5-*iso*propyl-2-thiohydantoin (0·095 g., theor., 0·085 g.) contaminated with a little starting material and hippuric acid (0·092 g.; theor., 0·099 g.).

Products of Alkaline Hydrolysis of 5-*Benzyl*-2-*thio*-1-*toluene*-p-*sulphonylglycylhydantoin*.—A solution of the acylthiohydantoin (0·094 g., 0·23 mmole) in 0·1N-sodium hydroxide (11 c.c.) was kept at 16° for 1 hour before acidification with dilute hydrochloric acid. The acid was neutralised with an excess of solid sodium hydrogen carbonate, and the neutral fraction extracted by ethyl acetate (5 × 30 c.c.). Acidification to pH 1 and a second ethyl acetate extraction of the aqueous phase then gave the acid fraction (0·052 g.; theor., 0·052 g.), which on recrystallisation from water had m. p. 147—148°, undepressed by authentic toluene-*p*-sulphonyl-

TABLE 1.

2-Thiohydantoin	M. p.	Yield [a] %	Formula	Found, %: C	H	N	Required, %: C	H	N
1-Benzoylglycyl	210—215° [b]	95	$C_{13}H_{11}O_3N_3S$	51·9	4·4	14·9	52·0	4·0	15·2
1-Benzoylglycyl-5-*iso*propyl	186—189	90	$C_{15}H_{17}O_3N_3S$	56·1	5·0	13·3	56·4	5·4	13·2
1-Benzoylglycyl-5-*iso*butyl	185—186	87 [c]	$C_{16}H_{19}O_3N_3S$	57·5	5·4	12·5	57·6	5·7	12·6
1-Benzoyl-DL-alanyl	187—188	100 [d]	$C_{13}H_{12}O_3N_3S$	53·9	5·0	14·3	53·6	4·5	14·4
1-Benzoyl-DL-leucyl	171—172 [e]	93	$C_{16}H_{19}O_3N_3S$	—	—	13·0	—	—	12·6

[a] Of crude material. [b] With decomp. The solution was never homogeneous and the product largely crystallised during the reaction. Schlack and Kumpf (*Z. physiol. Chem.*, 1926, **154**, 125) record m. p. 204—205° (decomp.). [c] A similar experiment with dimethylformamide as solvent instead of acetonitrile gave over 90% yield. [d] The reaction mixture became orange-yellow and the crystalline material was recovered in poor yield from the brown gum. [e] Schlack and Kumpf (*loc. cit.*) record m. p. 172—173°.

TABLE 2. *Stability of* 5-iso*butyl*-2-*thiohydantoin in* 0·01N-*alkali*.

Time (min.)	35	60	132	270
D (262 mμ)	0·389	0·356	0·325	0·290

TABLE 3. *Alkaline hydrolysis of* 1-*benzoylglycyl*-5-iso*butyl*-2-*thiohydantoin*.

Time (min.)	0	5	10	20	30	60
D (262 mμ)	0·180	0·306	0·309	0·327	0·320	0·297
D (278 mμ)	0·338	0·218	0·180	0·181	0·176	0·170
Density ratio	0·53	1·40	1·72	1·81	1·82	1·75

TABLE 4. *Alkaline hydrolysis of* 1-*benzoyl*-DL-*leucyl*-2-*thiohydantoin*.

Time (min.)	7	23	90
D (260 mμ)	0·305	0·345	0·322
D (278 mμ)	0·072	0·085	0·076
Density ratio	4·24	4·06	4·11

TABLE 5. *Alkaline hydrolysis of* 5-*benzyl*-2-*thio*-1-*toluene*-p-*sulphonylglycylhydantoin*.

Time (min.)	5	20	60	120	1050
D (260 mμ)	0·318	0·375	0·380	0·350	0·237
D (280 mμ)	0·310	0·236	0·210	0·238	0·205
Density ratio	1·08	1·67	1·92	1·55	1·22

glycine (m. p. 148°). Recrystallisation of the neutral fraction (0·048 g.; theor., 0·046 g.) from aqueous ethanol gave a yellow powder, m. p. 175—182° (Johnson and O'Brien, *J. Biol. Chem.*, 1912, **12**, 211, record m. p. 185° for 5-benzyl-2-thiohydantoin). Paper chromatography detected only glycine and only phenylalanine in hydrolysates of the acid (concentrated hydrochloric acid during 15 hours at 120°) and neutral (saturated aqueous barium hydroxide during 40 hours at 140°) fraction respectively.

When the acylthiohydantoin (0·208 g., 0·5 mmole) was kept during 20 minutes at 0° with 0·1N-sodium hydroxide (20 c.c.), hydrolysis was only 35% complete. The acylthiohydantoin (0·167 g., 0·4 mmole) was 20% hydrolysed in 24 hours at 16° by triethylamine (0·11 c.c., 0·8 mmole) in 50% aqueous ethanol (16 c.c.).

The authors thank Professor A. R. Todd, F.R.S., for his encouragement, Dr. N. S. Corby for information about some experiments with acyl phosphates, the Department of Scientific and Industrial Research for a Maintenance Grant (R. J. S.), and the Nuffield Trust for a Fellowship (H. G. K.) and for generous grants for chemicals.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 23rd*, 1952.]

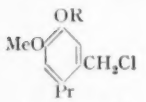
137. *The Chloromethylation of Eugenol and the Preparation of Some New* iso*Quinoline Bases.*

By G. R. CLEMO and R. W. TEMPLE.

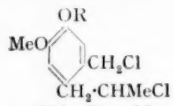
Various derivatives of eugenol have been chloromethylated. 4 : 5-Dimethoxy-2-propylbenzyl chloride has been used in the synthesis of a series of 1-substituted 3 : 4-dihydro-7 : 8-dimethoxy-5-propyl*iso*quinolines and related 1 : 2 : 3 : 4-tetrahydro*iso*quinolines. The chloromethylation products from β-chlorodihydroeugenol derivatives furnish 2-aryl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-3-methyl*iso*quinolines on condensation with aromatic amines.

IN continuation of work on eugenol (*J.*, 1945, 533; 1946, 701; 1947, 124, 613, 1692), the methyl ether and the benzoate of dihydroeugenol and of β-chlorodihydroeugenol have been chloromethylated smoothly at 60° by use of hydrochloric acid and formaldehyde, yielding (I—IV). All are stable solids except (III) which is an extremely viscous liquid.

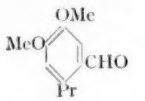
Attempts to orientate the chloromethyl compounds by oxidation were unsuccessful, except in the case of (I), which yielded an aldehyde different from 2 : 3-dimethoxy-5-propylbenzaldehyde on oxidation with potassium permanganate in acetone and must therefore be 4 : 5-dimethoxy-2-propylbenzaldehyde (V), showing that the chloromethyl group enters position 5 as expected. No trace of a second isomer was found in any of the reactions. The benzoyl group in (II) and (IV) remained intact in spite of the reaction's being carried out at 60° in saturated hydrochloric acid.



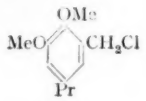
(I; R = Me)
(II; R = Bz)



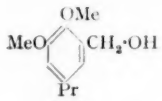
(III; R = Me)
(IV; R = Bz)



(V)



(VI)

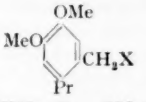


(VII)

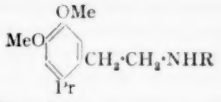
2 : 3-Dimethoxy-5-propylbenzyl chloride (VI) was made for comparison from methyl dihydroeugenol alcohol (VII) which was prepared from dihydroeugenol by the action of sodium hydroxide and formaldehyde, followed by methylation.

4 : 5-Dimethoxy-2-propylbenzyl chloride behaved similarly to 3 : 4-dimethoxybenzyl chloride on treatment with alcoholic potassium cyanide (Bide and Wilkinson, *Chem. and Ind.*, 1945, **64**, 84). Methanolic potassium cyanide gave only 4 : 5-dimethoxy-2-propylbenzyl methyl ether (VIII); aqueous-ethanolic potassium cyanide gave a small amount of the required cyanide (IX), which was eventually obtained in good yield by the method

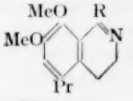
of Kindler and Gehlhaar (*Arch. Pharm.*, 1936, **274**, 377). Reduction of the benzyl cyanide (IX) over a platinum catalyst in acetic anhydride (Carothers and Jones, *J. Amer. Chem. Soc.*, 1925, **47**, 3051) was very slow and required a large amount of catalyst which had to be added in two parts or the resulting *N*-acetyl-2-phenylethylamine (X) was contaminated with unchanged cyanide. Reduction at higher pressures in alcohol saturated with ammonia and Raney nickel (Schwoegler and Adkins, *J. Amer. Chem. Soc.*, 1929, **61**, 3499) gave a good yield of the 2-phenylethylamine (XI). The acetyl (X), benzoyl (XII), phenylacetyl (XIII), and β-3 : 4-dimethoxybenzoyl (XIV) derivatives of the 2-phenylethylamine underwent the modified Bischler–Napieralski ring closure to give the corresponding dihydro*iso*quinolines (XV), (XVI), (XVII), (XVIII). The hydrochlorides of these were all extracted from a hydrochloric acid solution by chloroform and this method gave a much improved yield. Keeping 3 : 4-dihydro-7 : 8-dimethoxy-1-[2-(3 : 4-dimethoxyphenyl)ethyl]-5-propyl*iso*quinoline (XVIII) as its hydrochloride throughout the working up obviated the necessity of working under nitrogen, as the free base is unstable and undergoes rapid oxidation at room temperature to the ketone (XIX) which gave the characteristic Prussian-blue colour in boiling acetic anhydride. Reduction of (XV) and (XVIII) gave the corresponding tetrahydro*iso*quinolines (XXI) and (XXII). Dehydrogenation of the tetrahydro*iso*quinoline (XXII) in *p*-cymene with palladium black yielded the papaverine-type base (XXIV), as did dehydrogenation of the unstable base (XVIII) under nitrogen.



(VIII; X = OMe)
(IX; X = CN)

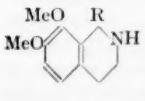


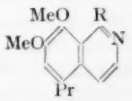
(X; R = Ac)
(XI; R = H)
(XII; R = Bz)
(XIII; R = CO·CH_2Ph)
[XIV; R = CO·CH_2·$C_6H_3(OMe)_2$]



(XV; R = Me)
(XVI; R = Ph)
(XVII; R = CH_2Ph)
[XVIII; R = CH_2·$C_6H_3(OMe)_2$]
[XIX; R = CO·$C_6H_3(OMe)_2$]
(XX; R = H)

(XXI; R = Me)
[XXII; R = CH_2·$C_6H_3(OMe)_2$]
(XXIII; R = H)

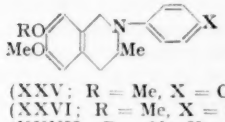




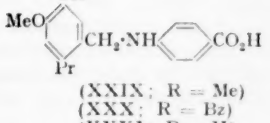
[XXIV; R = CH_2·$C_6H_3(OMe)_2$]

Attempts to prepare the parent dihydro*iso*quinoline (XX) by ring closure of the *N*-formyl derivative of (XI) were unsuccessful, as were attempts to prepare the tetrahydro*iso*quinoline (XXIII) by ring closure of the 2-phenylethylamine (XI) with formaldehyde or methylal and hydrochloric acid.

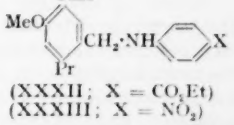
The only known practical method of preparing 2-aryl-1 : 2 : 3 : 4-tetrahydro*iso*quinolines is the condensation of 2-2′-bromoethylbenzyl bromide with aromatic amines (von Braun and Zobel, *Ber.*, 1923, **56**, 2142 : Holliman and Mann, *J.*, 1942, 737) and since this bromo-compound is obtained from *o*-toluidine in a maximum overall yield of 8·5% (Holliman and Mann, *loc. cit.*) the two chloromethyl compounds (III) and (IV) are of special interest.



(XXV; R = Me, X = CO_2H)
(XXVI; R = Me, X = CO_2Et)
(XXVII; R = Me, X = NO_2)
(XXVIII; R = Bz, X = CO_2H)



(XXIX; R = Me)
(XXX; R = Bz)
(XXXI; R = H)



(XXXII; X = CO_2Et)
(XXXIII; X = NO_2)

2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (III) can be prepared from eugenol in an overall yield of about 50% and, although the chlorine attached to the propyl group is rather unreactive, condensation occurs with primary aromatic amines in boiling pyridine, giving 2-aryl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy-3-methyl-

*iso*quinolines. With *p*-aminobenzoic acid, ethyl *p*-aminobenzoate, or *p*-nitroaniline the corresponding 2-aryltetrahydro*iso*quinolines (XXV, XXVI, and XXVII) were produced. With one or two mols. of *p*-aminobenzoic acid the same compound was obtained. 5-Benzoyloxy-2-2′-chloropropyl-4-methoxybenzyl chloride (IV) also condensed with *p*-aminobenzoic acid, to yield the tetrahydro*iso*quinoline (XXVIII) in rather poor yield. The corresponding open-chain compounds (XXIX—XXXIII) were made from the chloromethyl compounds (I) and (II).

Some of the above compounds have been submitted for physiological tests.

Experimental

Anhydrous sodium sulphate was used as drying agent.

4 : 5-*Dimethoxy*-2-*propylbenzyl Chloride*.—Dihydroeugenyl methyl ether (30 g.) was added to a mixture of aqueous formaldehyde (90 ml.; 40%) and concentrated hydrochloric acid (90 ml.), saturated with hydrogen chloride at 60°. The whole was stirred vigorously for 3·5 hours at 60° while hydrogen chloride was passed in. After cooling, the mixture was poured on ice, the liquor poured off, and the gummy organic layer taken up in ether, washed with water, dried and distilled, giving the *chloromethyl* compound (30·4 g.), b. p. 128—134°/2 mm., colourless prisms, m. p. 53—54° (from light petroleum) (Found: C, 62·5; H, 7·3; Cl, 15·8. $C_{12}H_{17}O_2Cl$ requires C, 63·0; H, 7·4; Cl, 15·5%).

Oxidation of 4 : 5-*Dimethoxy*-2-*propylbenzyl Chloride*.—Potassium permanganate (12 g.) was added during 2 hours to the chloromethyl compound (2 g.) and sodium carbonate (0·5 g.) in boiling acetone (100 ml.). The acetone was distilled off after 6 hours' boiling and the residue shaken with hot 2% potassium hydroxide solution. The undissolved yellow oil was extracted with ether, dried, and distilled, giving 4 : 5-*dimethoxy*-2-*propylbenzaldehyde* as a bright yellow oil, b. p. 117—120°/1 mm. (0·85 g.) (Found: C, 69·25; H, 7·7. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%). The 2 : 4-*dinitrophenylhydrazone* formed dark red needles, m. p. 199—201°, from ethanol–ethyl acetate (Found: C, 55·7; H, 5·4. $C_{18}H_{20}O_6N_4$ requires C, 55·7; H, 5·15%), depressed to 174° on admixture with 2 : 3-dimethoxy-5-propylbenzaldehyde dinitrophenylhydrazone (m. p. 200—201°).

5-*Benzoyloxy*-4-*methoxy*-2-*propylbenzyl Chloride*.—Dihydroeugenyl benzoate (20 g.) was chloromethylated in a similar fashion to dihydroeugenyl methyl ether. The *chloromethyl* compound (19·6 g.) forms colourless prisms, m. p. 97·5—99° from light petroleum (b. p. 80—100°) (Found: C, 68·0; H, 6·4; Cl, 10·8. $C_{18}H_{19}O_3Cl$ requires C, 67·8; H, 6·0; Cl, 11·1%).

β-*Chlorodihydroeugenyl Methyl Ether*.—Concentrated hydrochloric acid (110 ml.) was added to *O*-methyleugenol (28 g.) and then saturated with hydrogen chloride at 0°. After 6 days (occasional shaking and saturation with hydrogen chloride), the oil was extracted with chloroform, washed with sodium hydrogen carbonate solution and water, dried, and distilled, giving the *product*, b. p. 109—111°/1 mm. (26 g.) (Found: C, 61·5; H, 6·7. $C_{11}H_{15}O_2Cl$ requires C, 61·5; H, 7·0%).

2-2′-*Chloropropyl*-4 : 5-*dimethoxybenzyl Chloride*.—β-Chlorodihydroeugenyl methyl ether (17·7 g.) was chloromethylated for 4 hours at 60°. The *chloromethyl* compound is a very viscous oil, b. p. 144—146°/1 mm. (16·7 g.) (Found: C, 54·8; H, 6·1. $C_{12}H_{16}O_2Cl_2$ requires C, 54·7; H, 6·1%).

5-*Benzoyloxy*-2-2′-*chloropropyl*-4-*methoxybenzyl Chloride*.—β-Chlorodihydroeugenyl benzoate (15 g.) was chloromethylated at 60° for 4 hours. The *chloromethyl* compound (9·6 g.) forms prisms, m. p. 107—109°, from light petroleum (Found: C, 60·7; H, 5·25; Cl, 20·2. $C_{18}H_{18}O_3Cl_2$ requires C, 61·2; H, 5·1; Cl, 20·1%).

Action of Methanolic Potassium Cyanide on 4 : 5-*Dimethoxy*-2-*propylbenzyl Chloride*.—The benzyl chloride (5 g.) in dry methanol (50 ml.) was refluxed with potassium cyanide (1·6 g.) for 7 hours. The colourless precipitate was washed with methanol, the methanol removed, and the residue taken up in ether, washed with water, dried, and distilled, giving 4 : 5-*dimethoxy*-2-*propylbenzyl methyl ether*, b. p. 121—123°/0·2 mm. (4 g.) (Found: C, 70·0; H, 9·1. $C_{13}H_{20}O_3$ requires C, 69·6; H, 8·9%).

4 : 5-*Dimethoxy*-2-*propylbenzyl Cyanide*.—4 : 5-Dimethoxy-2-propylbenzyl chloride (23 g.) in benzene (50 ml.) was refluxed with potassium cyanide (15 g.) in water (70 ml.) for 3·5 hours with vigorous stirring. The benzene layer was separated, washed with water, and dried. Removal of the solvent and distillation gave the *cyanide* (19 g.), b. p. 153—155°/1 mm., colourless needles, m. p. 66—68° (from benzene–light petroleum) (Found: C, 71·3; H, 8·1. $C_{13}H_{17}O_2N$ requires C, 71·2; H, 7·8%)

Reduction of the Cyanide.—(a) *In acetic anhydride.* The above cyanide (7·3 g.) and platinum oxide (0·1 g.) in acetic anhydride (20 ml.) were shaken with hydrogen at 100 lb. per sq. in. After 20 hours, further catalyst (0·1 g.) was added and shaking with hydrogen continued for 20 hours. After filtration, the excess of acetic anhydride was decomposed by warm water, the resulting acetic acid removed, and the residual oil dissolved in benzene. Addition of light petroleum precipitated *N-acetyl-2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine* as needles (7·0 g.), m. p. 91—93°. Twice recrystallised from benzene–light petroleum it had m. p. 96—98° (Found : C, 67·95; H, 8·7. $C_{15}H_{23}O_3N$ requires C, 67·9; H, 8·7%). The amide was hydrolysed by boiling 40% hydrochloric acid (6 hours), and the resulting *2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine hydrochloride* crystallised from acetone–ethanol as plates, m. p. 241—243° (Found : C, 59·6; H, 8·4. $C_{13}H_{21}O_2N$,HCl requires C, 60·1; H, 8·5%).

2-(4 : 5-Dimethoxy-2-propylphenyl)ethylamine had b. p. 115—120°/0·1 mm., m. p. 43—46°. The *picrate* crystallised from aqueous alcohol in yellow prisms, m. p. 192—194° (Found : C, 50·8; H, 5·3. $C_{19}H_{24}O_9N_4$ requires C, 50·4; H, 5·3%).

(b) *By Raney nickel.* A solution of the benzyl cyanide (12 g.) in ethanol (100 ml.) was saturated with ammonia at 0° and reduced at 100°/100 atm. for 1·75 hours over Raney nickel (0·6 g.). Distillation gave 2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine (10 g.), identical with that obtained above.

*3 : 4-Dihydro-7 : 8-dimethoxy-1-methyl-5-propyl*iso*quinoline.*—*N*-Acetyl-2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine (1 g.) was refluxed in toluene (5 ml.) with phosphorus oxychloride (4 g.) for 2·5 hours with exclusion of moisture. The solution was diluted with light petroleum, and the precipitated gum washed with light petroleum and extracted with dilute hydrochloric acid. The acid solution was washed with benzene and basified (solid sodium carbonate). The precipitated oil was extracted with chloroform, dried, and distilled, giving the *dihydroisoquinoline*, b. p. 142—144°/2 mm. (0·6 g.) (Found : C, 72·65; H, 9·0. $C_{15}H_{21}O_2N$ requires C, 72·9; H, 8·5%). The *picrate* (from acetone–methanol) had m. p. 192—193° (Found : C, 52·4; H, 5·4. $C_{15}H_{21}O_2N,C_6H_3O_7N_3$ requires C, 52·9; H, 5·0%).

*1 : 2 : 3 : 4-Tetrahydro-7 : 8-dimethoxy-1-methyl-5-propyl*iso*quinoline.*—The dihydroisoquinoline hydrochloride (1·4 g.) was reduced over platinum at atmospheric pressure in 25% hydrochloric acid (35 ml.). The resulting *tetrahydroisoquinoline hydrochloride* crystallised from acetone–ether in prisms, m. p. 167—169° (1·25 g.) (Found : C, 63·0; H, 8·6. $C_{15}H_{24}O_2NCl$ requires C, 63·05; H, 8·4%). The *picrate* (from ether–methanol) had m. p. 158—160° (Found : C, 53·1; H, 5·8. $C_{15}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 52·7; H, 5·4%).

N-Benzoyl-2-(4 : 5-dimethoxy-2-propylphenyl)ethylamine.—Benzoyl chloride (1 ml.) was added slowly to the amine (1·1 g.) suspended in sodium hydroxide solution (15 ml.; 10%), with stirring, and the white solid which separated recrystallised from benzene–light petroleum (b. p. 60—80°), giving the *amide* (1 g.) as needles, m. p. 117—118·5° (Found : C, 73·3; H, 8·1. $C_{20}H_{25}O_3N$ requires C, 73·4; H, 7·65%).

*3 : 4-Dihydro-7 : 8-dimethoxy-1-phenyl-5-propyl*iso*quinoline Hydrochloride.*—The foregoing amide (1 g.) was refluxed in toluene (4 ml.) with phosphorus oxychloride (3·2 g.) for 3·5 hours, then cooled, the solution was diluted with light petroleum, and the precipitated gum washed with light petroleum and extracted with hot 30% hydrochloric acid. The acid solution was extracted three times with chloroform. The extracts were dried and evaporated, leaving the *hydrochloride* (0·9 g.), which formed yellow prisms, m. p. 192·5—194° (decomp.), from acetone (Found : C, 69·8; H, 7·4. $C_{20}H_{24}O_2NCl$ requires C, 69·5; H, 6·95%). The base was obtained as a glass. The *picrate*, from methanol–ether, forms prisms, m. p. 144—146° (Found : C, 57·95; H, 5·0. $C_{20}H_{23}O_2N,C_6H_3O_7N_3$ requires C, 58·0; H, 4·8%). The *methiodide* crystallised from acetone as small yellow needles, m. p. 184—185° (Found : C, 55·6; H, 6·0. $C_{21}H_{26}O_2NI$ requires C, 55·9; H, 5·8%).

2-(4 : 5-Dimethoxyphenyl-2-propyl)-N-phenylacetylethylamine.—Phenylacetyl chloride (1·25 ml.) was added to the ethylamine (1·5 g.) suspended in 10% sodium hydroxide solution (15 ml.). The *amide* which separated crystallised from benzene–light petroleum as needles, m. p. 94—96° (1·4 g.) (Found : C, 73·8; H, 8·2. $C_{21}H_{27}O_3N$ requires C, 73·9; H, 7·9%).

*1-Benzyl-3 : 4-dihydro-7 : 8-dimethoxy-5-propyl*iso*quinoline Hydrochloride.*—The foregoing amide (1 g.) in chloroform (8 ml.) was refluxed with phosphorus oxychloride (2 ml.) for 3·5 hours, the solvent and excess of oxychloride were removed, the residue was washed with light petroleum and dissolved in methanol, and water added to incipient cloudiness. Basification with sodium carbonate precipitated a yellow oil which was extracted with chloroform, dried, and evaporated. Hydrogen chloride was passed through an ethereal solution of the base and the precipitated yellow *hydrochloride* crystallised from acetone–ether as pale yellow prisms,

m. p. 155—156° (decomp.) (0·4 g.) (Found: C, 69·9; H, 7·3. $C_{21}H_{26}O_2NCl$ requires C, 70·1; H, 7·2%). The base crystallised from aqueous methanol in prisms, m. p. 97—99°. The *picrate*, prisms (from methanol), had m. p. 127—128·5° (Found: C, 58·7; H, 5·3. $C_{21}H_{25}O_2N,C_6H_3O_7N_3$ requires C, 58·7; H, 5·1%). The *methiodide* crystallised from acetone in bright yellow prisms, m. p. 131—132·5° (Found: C, 56·6; H, 6·2. $C_{22}H_{28}O_2NI$ requires C, 56·8; H, 6·0%).

N-(3 : 4-*Dimethoxyphenyl*)*acetyl*-2-(4 : 5-*dimethoxy*-2-*propylphenyl*)*ethylamine*.—The acid chloride (from 9 g. of homoveratric acid) in benzene (20 ml.) was added with stirring to the ethylamine (8·5 g.) suspended in 15% potassium hydroxide (80 ml.). The buff-coloured precipitate crystallised from benzene–light petroleum (b. p. 60—80°) (charcoal) as colourless needles, m. p. 119—120° (11 g.) (Found: C, 68·9; H, 8·1. $C_{23}H_{31}O_5N$ requires C, 68·8; H, 7·7%).

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*iso*quinoline Hydrochloride*.—The foregoing amide (5 g.) in chloroform (40 ml.) was refluxed with phosphorus oxychloride (15 ml.) for 1·5 hours. The solvent was removed, the residual gum washed with light petroleum and extracted four times with hot 30% hydrochloric acid, and the acid extract washed with ether, extracted with chloroform, and dried. Removal of the chloroform left a yellow gum, which dissolved in acetone and was precipitated by ether, giving the *hydrochloride* (4 g.) as yellow prisms, m. p. 154—158° (decomp.), raised by recrystallisation from acetone–ether to m. p. 161—163° (3·75 g.) (Found: C, 66·0; H, 7·4. $C_{23}H_{30}O_4NCl$ requires C, 65·8; H, 7·15%). The *picrate* crystallised from methanol as prisms, m. p. 131—134° (Found: C, 57·2; H, 5·7. $C_{23}H_{29}O_4N,C_6H_3O_7N_3$ requires C, 56·9; H, 5·2%).

3 : 4-*Dihydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzoyl*)-5-*propyl*iso*quinoline*.—The foregoing hydrochloride (0·3 g.) in water was basified with potassium carbonate, the free base extracted with ether and dried, and the ether removed. The residual slightly yellow oil was dissolved in methanol and set aside in an open vessel at room temperature. Soon small colourless prisms appeared. After 20 hours more methanol was added and the yellow solution treated with charcoal; most of the methanol was removed and water added to incipient cloudiness. Cooling gave the oxidised *base* as cubes, m. p. 138—140° (108 mg.), raised to 139—141° by crystallisation from aqueous methanol (Found: C, 69·9; H, 7·0. $C_{23}H_{27}O_5N$ requires C, 69·5; H, 6·8%). A trace of the base in acetic anhydride developed a Prussian-blue colour on boiling. The *picrate* (from methanol) formed prisms, m. p. 167—169° (Found: C, 55·25; H, 5·1. $C_{23}H_{27}O_5N,C_6H_3O_7N_3$ requires C, 55·6; H, 4·8%). The *methiodide* crystallised from acetone–ether as orange prisms, m. p. 170—173° (Found: C, 53·4; H, 6·1. $C_{24}H_{30}O_5NI$ requires C, 53·4; H, 5·6%).

1 : 2 : 3 : 4-*Tetrahydro*-7 : 8-*dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*iso*quinoline*.—The corresponding dihydro*iso*quinoline hydrochloride (1·3 g.) in water (50 ml.) was shaken with hydrogen at one atm. over platinum. After 2·5 hours the hydrogen uptake was 98%. Filtration, concentration, and basification precipitated a gum which was isolated by means of ether. It crystallised from light petroleum (b. p. 60—80°), giving the *tetrahydro*iso*quinoline* as colourless needles, m. p. 84—86° (0·9 g.) (Found: C, 71·5; H, 8·5. $C_{23}H_{31}O_4N$ requires C, 71·7; H, 8·05%). The *hydrochloride* crystallised from acetone as needles, m. p. 178—180° (Found: C, 65·4; H, 7·9. $C_{23}H_{32}O_4NCl$ requires C, 65·5; H, 7·6%). The *picrate* formed needles, m. p. 181—183°, from ethanol (Found: C, 56·6; H, 5·6. $C_{23}H_{31}O_4N,C_6H_3O_7N_3$ requires C, 56·7; H, 5·5%).

7 : 8-*Dimethoxy*-1-(3 : 4-*dimethoxybenzyl*)-5-*propyl*iso*quinoline Hydrochloride*.—(a) *From the tetrahydro*iso*quinoline*. The tetrahydro*iso*quinoline (0·2 g.) and palladium black (0·15 g.) in *p*-cymene (3 ml.) were refluxed for 24 hours. The *p*-cymene was removed in a vacuum and the residual yellow oil extracted with hot 25% hydrochloric acid. The acid extract was washed with ether and extracted with chloroform, dried, and evaporated, leaving a yellow glass which was dissolved in acetone. Addition of ether precipitated the iso*quinoline hydrochloride* as light yellow prisms (80 mg.), m. p. 176—178° (decomp.), raised to 179—180° (decomp.) by crystallisation from acetone–ether (Found: C, 65·7; H, 7·05. $C_{23}H_{27}O_4NHCl$ requires C, 66·1; H, 6·7%). The *picrate* formed prisms, m. p. 157—158·5°, from methanol (Found: C, 57·3; H, 4·7. $C_{23}H_{27}O_4N,C_6H_3O_7N_3$ requires C, 57·1; H, 4·9%). When this hydrochloride was shaken in water with hydrogen and platinum two mols. were absorbed, and the tetrahydro*iso*quinoline hydrochloride obtained had m. p. and mixed m. p. 172—175°.

(b) *From the dihydro*iso*quinoline*. A solution of 3 : 4-dihydro-7 : 8-dimethoxy-1-(3 : 4-dimethoxybenzyl)-5-propyl*iso*quinoline hydrochloride (0·3 g.) in water was basified with potassium carbonate, and the precipitated oil quickly extracted with ether and dried. The ether was removed in nitrogen and the residual oil refluxed in *p*-cymene (4 ml.) with palladium black

(0·1 g.) under nitrogen for 10 hours. The product was worked up as in (*a*), giving, after two crystallisations from acetone–ether, the *iso*quinoline hydrochloride, m. p. 177—178° (120 mg.), identical with the product obtained as in (a).

p-(4 : 5-*Dimethoxy*-2-*propylbenzylamino*)*benzoic Acid.*—4 : 5-Dimethoxy-2-propylbenzyl chloride (1 g.) and *p*-aminobenzoic acid (0·7 g.) in pyridine (2 ml.) were boiled for 3 minutes, cooled, and diluted with water, and the precipitated gum was rubbed until solid. Recrystallisation from aqueous ethanol gave the *amino-acid* as prisms, m. p. 199—201° (Found : C, 69·2; H, 7·5. $C_{19}H_{23}O_4N$ requires C, 69·3; H, 7·0%).

2-p-*Carboxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*isoquinoline.—2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (2 g.) and *p*-aminobenzoic acid (1 g., 1 equiv.) in pyridine (4 ml.) were refluxed for 1·5 hours. The cooled solution was poured on ice, and the precipitated gum washed with water and rubbed with methanol till solid (0·8 g.). Two crystallisations from methanol (charcoal) gave the *product* as cream-coloured prisms, m. p. 220—223° (Found : C, 69·8; H, 6·5%; equiv., 329. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·4%; equiv., 327).

The same experiment with 2 equivs. of *p*-aminobenzoic acid gave the same product, m. p. and mixed m. p. 219—222°.

p-(4 : 5-*Dimethoxy*-2-*propylbenzylamino*)*ethyl Benzoate.*—The chloride (2 g.) and ethyl *p*-aminobenzoate (1·5 g.) in boiling pyridine (4 ml.) (3 hours) gave the substitued *ester* as prisms, m. p. 100—102° (from methanol) (Found : C, 70·9; H, 7·9. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6%).

2-p-*Carbethoxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*isoquinoline.—2-2′-Chloropropyl-4 : 5-dimethoxybenzyl chloride (2·6 g.) and ethyl *p*-aminobenzoate (1·7 g.) in pyridine (5 ml.) were refluxed for 1·75 hours. The *tetrahydro*isoquinoline crystallised from methanol as plates, m. p. 139—141° (1 g.) (Found : C, 71·1; H, 7·2. $C_{21}H_{25}O_4N$ requires C, 71·0; H, 7·0%).

N-(4 : 5-*Dimethoxy*-2-*propylbenzyl*)-p-*nitroaniline.*—Prepared from the chloride (2 g.) and *p*-nitroaniline (1·4 g.) in boiling pyridine (1 hour), this *base* crystallised from methanol in yellow prisms (1·1 g.), m. p. 147·5—149·5° (Found : C, 65·3; H, 6·9. $C_{18}H_{22}O_4N_2$ requires C, 65·45; H, 6·7%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxy*-3-*methyl*-2-p-*nitrophenyl*isoquinoline.—*p*-Nitroaniline (1·8 g.) and 2-2′-chloropropyl-4 : 5-dimethoxybenzyl chloride (3 g.) in pyridine (7 ml.) were refluxed for 1·5 hours. The tetrahydro*iso*quinoline, worked up as above, formed yellow prisms, m. p. 157—159° (0·5 g.), from methanol (Found : C, 65·8; H, 6·5. $C_{18}H_{20}O_4N_2$ requires C, 65·85; H, 6·1%).

p-(5-*Benzoyloxy*-4-*methoxy*-2-*propylbenzylamino*)*benzoic Acid.*—*p*-Aminobenzoic acid (1 g.) and 5-benzoyloxy-4-methoxy-2-propylbenzyl chloride (2 g.) in pyridine were refluxed for 1·5 hours. The *product* crystallised from methanol in prisms, m. p. 220—222° (Found : C, 71·8; H, 5·95. $C_{25}H_{25}O_5N$ requires C, 71·6; H, 6·0%).

p-(5-*Hydroxy*-4-*methoxy*-2-*propylbenzylamino*)*benzoic Acid.*—The foregoing benzoate (8 g.) in alcohol (75 ml.) was refluxed with sodium hydroxide (10 g.) in water (35 ml.) for 2·5 hours. Evaporation, dilution with water, washing with chloroform, acidification to pH 6 with concentrated hydrochloric acid, and crystallisation of the precipitate (5·3 g.) twice from benzene (charcoal) and once from aqueous alcohol gave the acid as plates, m. p. 162—164° (Found : C, 68·7; H, 7·0. $C_{18}H_{21}O_4N$ requires C, 68·6; H, 6·7%).

7-*Benzoyloxy*-2-p-*carboxyphenyl*-1 : 2 : 3 : 4-*tetrahydro*-6-*methoxy*-3-*methyl*isoquinoline.—A solution of 5-benzoyloxy-2-2′-chloropropyl-4-methoxybenzyl chloride (7·5 g.) and *p*-aminobenzoic acid (3·3 g.) in pyridine (13 ml.) was refluxed for 4 hours, cooled, and poured on crushed ice. The precipitated yellow solid was washed with water and treated with charcoal in acetone. Removal of most of the acetone and cooling gave the *tetrahydro*isoquinoline as prisms (0·95 g.), m. p. 212—215° (after recrystallisation) (Found : C, 72·1; H, 5·9. $C_{25}H_{23}O_5N$ requires C, 71·9; H, 5·5%).

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138. *The Influence of Conjugation on the Ionization of Aromatic Amines.*

By N. S. Hush.

The energy changes attending ionization of aromatic mono- and di-amines are discussed. Where the main variable factor controlling ionization may be taken to be the change in π-electron energy on addition of a proton, the variations of dissociation constant can be understood in terms of LCAO molecular orbital and first-order perturbation theory. In particular, it becomes clear why differences in energy of ionization amongst bases of these types are so much smaller than for proton addition to nuclear nitrogen in isoconjugate heteroaromatic amines. The types of energy change for the different ionizations are examined, and approximate values of some Coulomb integrals are obtained. The energetics of prototropic reactions involving aminium ions are also considered.

The electron densities of 15 dicarbanions are given in an appendix.

In this paper, the ionization constants of aromatic monoamines and diamines are correlated with the differences in π-electron energy between the proton donors and acceptors of the acid–base systems. There are two main assumptions underlying this procedure: the first that the difference in standard free energy of ionization of two bases of similar charge distribution in a given solvent at a fixed temperature is equal to the difference of potential energy accompanying proton addition in the gas phase, *i.e.*, to the difference of proton affinity of the molecules; and the second that, for these compounds, the change of potential energy ΔE_p accompanying proton addition in the gas phase is equal to the difference in unsaturation energy $\Delta\varepsilon$ between donor and acceptor plus a constant term, *i.e.*, that the proton affinity E_h of such a molecule in the gas phase is given by $E_h = E_h^\circ + \Delta\varepsilon$, where E_h° is a constant.

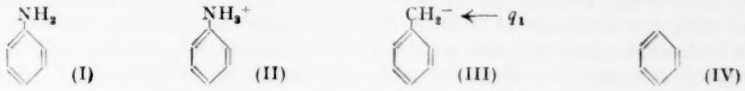
Although neither assumption can be strictly correct, it is probable that neither is so much in error that the general correlations of features of electronic structure with basic strength, which are at best semi-quantitative, will be invalidated. This is supported by the reasonable correlation with experimental data of the analogous treatment of proton addition to heterocyclic amines by Longuet-Higgins (*J. Chem. Physics*, 1950, **18**, 275, hereafter referred to as Ref. 1). Wheland's discussion of hydrocarbon ionization (*ibid.*, 1934, **2**, 474) is also of interest in this connection. On this basis, we may write as a fair approximation:

$$\varepsilon_{donor} - \varepsilon_{acceptor} = \text{const.} - 2{\cdot}3\boldsymbol{R}T\mathrm{p}K_a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

The unsaturation energies of donor and acceptor ions and molecules have been calculated by a combination of LCAO molecular orbital and first-order perturbation theory. Non-orthogonality of adjacent atomic orbitals has been neglected; this will not lead to serious error for these systems (cf. Coulson and Chirgwin, *Proc. Roy. Soc.*, 1950, *A*, **201**, 196).

Electronic Structure.—It is assumed that the proton donors and acceptors are isoconjugate with (*i.e.*, contain the same number of π-electrons in approximately the same geometrical configuration of atomic *p*-orbitals as) the hydrocarbons obtained by replacing NH_3^+ by H and NH_2 by CH_2^-; *e.g.*, in the simplest case, (I) and (II) are isoconjugate with (III) and (IV), respectively. This representation ignores the possibility of hyperconjugation of NH_3^+, which is reasonable to this approximation. It assumes also that the NH_2 group conjugates with the aromatic residue, and that the magnitude of the N Coulomb and NC resonance integrals are such that this group may be treated in first-order approximation as a perturbed CH_2^-. These assumptions, although usual, merit brief discussion. It is certain that considerable delocalization of NH_2 and NR_2 nonbonding electrons occurs when these groups are attached to aromatic or heteroaromatic residues. The most direct evidence for this (at least in monoamines) is provided by the marked effects of *o*-substituents which are large enough to twist the amino-group out of

the aromatic plane on the frequency and intensity of electronic transitions (Remington, *J. Amer. Chem. Soc.*, 1945, **67**, 1838; Klevens and Platt, *ibid.*, 1949, **71**, 1714) and on the dipole moments (Ingham and Hampson, *J.*, 1939, 981) of the molecules. Also, it has long been recognized that the basicity of an aromatic amine can be increased by a predominantly steric effect by introduction of bulky *o*-substituents (Davies and Addis, *J.*, 1937, 1622), and the highest pK known for an aromatic monoamine is for a sterically-hindered molecule of this type, *viz.*, *NN*-diethyl-*o*-toluidine, pK 7·2 (cf. Albert, *Chem. and Ind.*, 1947, 51). Since dipole measurements on *p*-diamines (Bretscher, *Helv. Phys. Acta*, 1928, **1**, 355; Williams and Weissberger, *J. Amer. Chem. Soc.*, 1928, **50**, 2332; Weissberger and Sängewald, *Z. physikal. Chem.*, 1929, *B*, **5**, 237; Linke, *ibid.*, 1940, **46**, 261) show that the NH_2 groups are far from flat in molecules of this sort, a considerable approximation is involved



(I) (II) (III) (IV)

in treating the N wave-function as pure $2p\pi$.* However, this wave-function has sufficient π-character to conjugate strongly with an aromatic ring, so that it is reasonable to suppose that (to first-order approximation) deviations from trigonal hybridization can be regarded as part of the perturbation H' applied to the one-electron Hamiltonian of the hydrocarbon analogue by nitrogen substitution. This assumption is justified *a posteriori* by the success of treatments of related phenomena in which it is implicit (see Longuet-Higgins, Ref. 1; Longuet-Higgins, Rector, and Platt, *J. Chem. Phys.*, 1950, **18**, 1174; Hush, *ibid.*, 1952, **20**, 1660).

Calculation of Unsaturation Energies.—Where $e_H{}^j$ is the energy of a π-electron in the MO ψ^j of the isoconjugate hydrocarbon ($\psi^j = \Sigma c_r{}^j\phi_r$), the energy e^j in the nitrogen-substituted molecule is, to first-order approximation,

$$e^j = e_H{}^j + \sum_r\sum_s c_r{}^j c_s{}^j \int \phi_r H' \phi_s{}^* d\tau$$

Assuming that integrals other than Coulomb terms of the type $\int \phi_r H' \phi_r{}^* d\tau = \delta\alpha_r$ are small enough to be ignored,† and summing over all π-electrons, we obtain (cf. Ref. 1)

$$\varepsilon - \varepsilon_{(H)} = \sum_r q_r \delta\alpha_r \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where ε is the unsaturation energy of the amine molecule or ion, $\varepsilon_{(H)}$ is that of the isoconjugate hydrocarbon, and q_r is the π-electron density at atom r in the hydrocarbon. Unless otherwise specified, energy terms are expressed in units of β_{CC}, the CC resonance integral.

The two important $\delta\alpha_r$ terms to be taken into account are y, the difference in Coulomb integral between NH_2 and CH_2, and z, the change in Coulomb integral of carbon in the aromatic $\geqslant$CH grouping when H is replaced by $NH_3{}^+$. (The small change in Coulomb integral of the ring carbon atom on substitution of NH_2 can be ignored in this approximation.) Thus, the unsaturation energy change $\Delta\varepsilon$ accompanying addition of a proton to an amine can be expressed as :

$$\Delta\varepsilon = \varepsilon_{donor} - \varepsilon_{acceptor} = \varepsilon_{(H)\ donor} - \varepsilon_{(H)\ acceptor} - f(y) - g(z).$$

The term $\varepsilon_{(H)\ donor} - \varepsilon_{(H)\ acceptor}$ will be written for brevity as $-\varepsilon_{conj.}$; and substituting in eqn. (1) we have, for any amine,

$$2{\cdot}3\,\boldsymbol{R}T\mathrm{p}K = \varepsilon_{conj.} + f(y) + g(z) + A \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where A is a constant. In the case of diamines, a small statistical correction must be made to the constant A, since, where there is no interaction between the amino-groups in a symmetrical diamine, the statistical ratio K_2/K_1 is 4, whence $pK_1 - pK_2 = 0{\cdot}6$ unit

* For discussion, see Sklar, *J. Chem. Phys.*, 1939, **7**, 984; Goeppert-Mayer and McCallum, *Rev. Mod. Phys.*, 1942, **14**, 248; Coulson, "Valence," Oxford, 1952, p. 246. The uncertainty introduced into the MO treatment by this effect has been mentioned by de Heer (Thesis, Amsterdam, 1950, p. 70) and by Coulson and de Heer (*J.*, 1952, 483).

† The validity of this assumption is discussed below.

(cf. Greenspan, *Chem. Reviews*, 1933, **12**, 339). [This appears to hold for crystal-violet, for which $K_2/K_1 = 4{\cdot}08 \pm 5\%$ (Adams and Rosenstein, *J. Amer. Chem. Soc.*, 1914, **36**, 1452).]

In applying eqn. (3), it will be assumed that the isoconjugate hydrocarbon is always an alternant molecule, *i.e.*, one containing no odd-membered rings (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1947, *A*, **191**, 39); in all cases, the extension to non-alternant systems is obvious.

The values of the Coulomb terms y and z are fixed, but the functions $f(y)$ and $g(z)$ differ according as the proton acceptor is a monoamine, a diamine mono-ion, or a diamine.

(a) *Monoamines.* In this case,

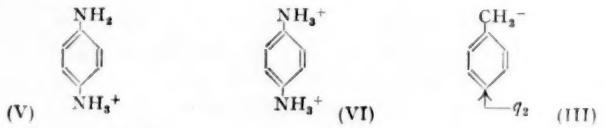
$$f(y) = q_1 y,\ g(z) = -z$$

where q_1 is the π-electron density at the extracyclic position in the monocarbanion isoconjugate with the acceptor [cf. (III)]. The carbanion contains one non-bonding MO, while the hydrocarbon isoconjugate with the proton acceptor contains no such MO; since the discussion is limited to alternant molecules it follows (Coulson and Rushbrooke, *Proc. Camb. Phil. Soc.*, 1940, **36**, 193) that $g(z) = -z$.

(b) *Second ionization of diamines* (K_2). Here a proton is added to a diamine mono-ion, *e.g.*, (V) + $H^+ \longrightarrow$ (VI). Hence for this ionization,

$$f(y) = q_1 y,\ g(z) = (q_2 - 2)z$$

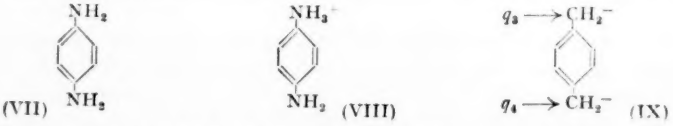
where q_2 is the π-electron density in the carbanion isoconjugate with the acceptor at the position of substitution of NH_3^+. [In the above example, this is the position in (III) marked with an arrow.]



(c) *First ionization of diamines.* The acceptor in this reaction is the donor of the corresponding second ionization, as *e.g.*, (VII) + $H^+ \longrightarrow$ (VIII). Hence

$$f(y) = (q_3 + q_4 - q_1)y,\ g(z) = -q_2(z)$$

where q_3 and q_4 are the π-electron densities at the extracyclic carbon atoms in the dicarbanion isoconjugate with the diamine [*e.g.*, (IX)]. The dicarbanion may or may not contain non-bonding MO.



The values of $\varepsilon_{conj.}$, $f(y)/y$, $g(z)/z$, and pK are tabulated in the Table for all systems for which reliable data are available.

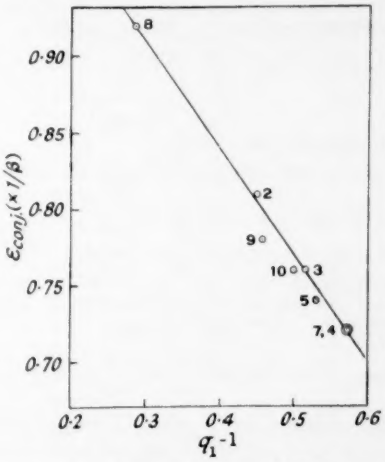
Magnitude of Perturbation Terms.—In order to test the theory, values of the Coulomb terms y and z are required. The magnitude of y should not differ greatly from the corresponding value of $\delta\alpha_r$ for heterocyclic nitrogen; typical values proposed for this term are 1·0 (Brown, *Quart. Reviews*, 1952, **6**, 1) and 0·6 (Löwdin, *J. Chem. Phys.*, 1951, **19**, 1323). In order to obtain a value appropriate to these systems from the experimental data, it is necessary to express $\varepsilon_{conj.}$ in absolute units, and the usual value of β_{CC} = *ca.* −20·0 kcals. mole^{-1} (cf. Wheland, *J. Amer. Chem. Soc.*, 1941, **63**, 2025) is assumed. For monoamines, a plot of $2{\cdot}3\boldsymbol{R}T\text{p}K - \varepsilon_{conj.}$ against q_1 yields a fairly straight line of negative gradient, which, according to eqn. (3), should be y. The value found in this way is −13 kcal. mole^{-1} or 0·65β. This value has been assumed in all subsequent calculations.

Since an aromatic carbon atom will have less electronic charge when bound to NH_3^+ than when bound to H, z should also be negative, and on general grounds (Coulson and Dewar, *Discuss. Faraday Soc.*, 1947, **2**, 57), z would be expected to be of the order of ~0·5β.

A value of z has been found from the plot of $2{\cdot}3\boldsymbol{R}T\mathrm{p}K_1 - \varepsilon_{\mathrm{conj.}} - \mathrm{f}(y)$ against q_2 for the first ionization of diamines; this yields $z = ca.\ -9$ kcal. mole^{-1}, or $0{\cdot}45\beta$. The value is reasonable, and is assumed in subsequent calculations.*

Comparison with Experimental Ionization Data.—The Table contains the appropriate data for a number of amines and diamines. For a direct test of the theory, it has been thought best to list observed and calculated differences of pK for an amine from those for a standard amine; this avoids the introduction of further parameters. The amine chosen arbitrarily as standard is β-naphthylamine.

The calculated and observed pK values in the last two columns of the Table show a general parallelism which is as close an agreement as can be expected in this approximate treatment. Large deviations are found only for the diamines (16, 21) in which the amino-groups are in the *o*-position to each other or (to a lesser extent) in the *peri*-position (20); special effects of this sort are well-known for aromatic base systems (Albert and Goldacre, *J.*, 1946, 706). Apart from these extreme cases, energy and entropy terms arising from the proximity of the two groups are not large enough to upset the trends of pK



Extracyclic electron densities and conjugation energies of aromatic methyl radicals.

Numbering as in the Table for 2, 3, 4, 5, and 7, with addition of 9-anthrylmethyl (8), 4-stilbenylmethyl (9), and 4-styrylmethyl (10). Sources of energy data are those given in the Table.

with structure predicted by eqn. (3); in particular, the effect of a charged NH_3^+ group on the distribution of H^+ ions about a diamine mono-ion in solution on the second ionization of the base appears to be small. The magnitudes of similar effects in dicarboxy-compounds have been discussed by Greenspan (*loc. cit.*).

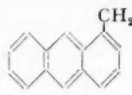
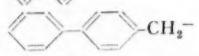
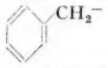
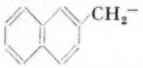
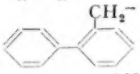
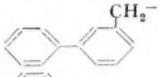
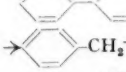
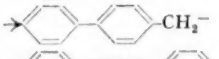
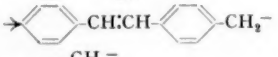
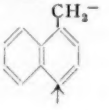
Discussion.—The most striking feature of the ionization of aromatic monoamines is the very small variation in pK in a range of molecules in the hydrocarbon analogues of which there is a reasonably large variation in conjugation energy and charge density of the extracyclic atom. This approximate constancy is in marked contrast to the very large variations of dissociation constant for addition to the ring-nitrogen atom of heteroaromatic amines such as aminoacridines (Albert, "The Acridines," Edward Arnold & Co., 1951, Chap. IX) and aminoquinolines with similar changes in charge density at the position of proton-addition. This suggests a compensation of competing effects for molecules of the former type; and in fact, the main reason for the lack of variation of K for monoamines is that in carbanions of the type $Ar{-}CH_2^-$, where Ar is an aromatic residue, the conjugation energy of the extracyclic group is a linear function of q_1, such that increase in conjugation energy is always accompanied by decrease in q_1. This linear relation is illustrated in the Figure.

The fundamental relation here is that between the conjugation energy and the modulus

* The difference of intercepts for the plots for monoamines and second diamine ionization yields approximately the same value. That z is small is shown by the small effect of NH_3^+ substitution on the ultra-violet absorption envelope of the hydrocarbon (Jones, *Chem. Reviews*, 1943, **32**, 1; Sklar, *loc. cit.*).

of the extracyclic AO coefficient in the non-bonding MO of the radical, which is similarly linear. This relation can be understood theoretically, and will be discussed elsewhere.

The gradient in the figure indicates that, since y is negative and of the same order as β_{CC}, in monoamines base-weakening increase in conjugation energy of the CH_2^- group is always compensated by base-strengthening decrease in π-electron density at this position in the carbanion; the approximate constancy of pK is thus understandable.

Amine	No.	Carbanion*	$\varepsilon_{conj.}$	$f(y)/y$	$g(z)/z$	pK_f	pK–pK(β-$C_{10}H_7{\cdot}NH_2$): obs.	calc.
1-Anthrylamine	1		0·84[a]	1·381	−1	$4{\cdot}1_{25}$[c]	−0·2	−0·1
α-Naphthylamine	2		0·81	1·450	−1	$4{\cdot}10_{22}$[d]	−0·2	−0·3
p-Aminodiphenyl	3		0·76	1·516	−1	$4{\cdot}38_{18}$[e]	0·1	−0·2
Aniline	4		0·72	1·572	−1	$4{\cdot}67_{21}$[d]	0·4	−0·1
β-Naphthylamine	5		0·74	1·529	−1	$4{\cdot}25_{23}$[d]	0	0
o-Aminodiphenyl	6		0·76[a]	1·516	−1	$3{\cdot}85_{18}$[e]	−0·4	−0·2
m-Aminodiphenyl	7		0·72	1·572	−1	$4{\cdot}28_{17}$[e]	0	−0·1
p-Phenylenediamine$_2$	8		0·72	1·572	−0·857	$3{\cdot}11_{25}$[f]	−1·1	−1·1
Benzidine$_2$	9		0·76	1·516	−0·968	$3{\cdot}85_{25}$[g]	−0·4	−0·4
Stilbene-*pp*′-diamine$_2$	10		0·78	1·457	−0·971	~$3{\cdot}9_{25}$[c]	−0·4	−0·1
1 : 4-Naphthylenediamine$_2$	11		0·81	1·450	−0·800	$2{\cdot}78_{25}$[c]	−1·5	−1·6
p-Phenylenediamine$_1$	12	A	0·58	1·758	−1·143	$6{\cdot}34_{25}$	2·1	1·7
Stilbene-*pp*′-diamine$_1$	13	O	0·74	1·563	−1·029	~$5{\cdot}2_{25}$[c]	1·0	0·5
1 : 4-Naphthylenediamine$_1$	14	D	0·59	1·778	−1·200	$5{\cdot}87_{25}$[c]	1·6	1·7
m-Phenylenediamine$_1$	15	B	0·72[b]	1·594	−1	$5{\cdot}02_{20}$[h]	0·8	0·3
o-Phenylenediamine$_1$	16	C	0·65	1·608	−1·143	$4{\cdot}60_{20}$[i]	(0·4 *ortho-*)	2·1)
Benzidine$_1$	17	N	0·71	1·598	−1·032	$4{\cdot}95_{25}$[g]	0·7	0·6
1 : 5-Naphthylenediamine$_1$	18	H	0·75	1·586	−1·050	$4{\cdot}70_{20}$[j]*	0·2 †	0·2
1 : 4-Naphthylenediamine$_1$	19	D	0·59	1·778	−1·200	$5{\cdot}54_{21}$[j]	1·6	1·7
1 : 8-Naphthylenediamine$_1$	20	G	0·77	1·576	−1	$4{\cdot}29_{17}$[j]	(0·4	−0·3)
2 : 3-Naphthylenediamine$_1$	21	F	0·77	1·419	−1·059	$3{\cdot}54_{21}$[j]	(−0·4 *peri-*, *ortho-*	1·6)
2 : 6-Naphthylenediamine$_1$	22	J	0·68	1·653	−1·059	$4{\cdot}93_{20}$[j]	1·0	0·7
2 : 7-Naphthylenediamine$_1$	23	K	0·76	1·533	−1	$4{\cdot}55_{18}$[j]	0·6	0·3

* The carbanions corresponding to 12—23 are given in the appendix.

[Footnotes on p. 689]

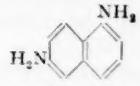
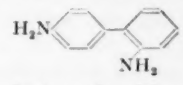
It will be noticed that there is much more variation of pK_1 of diamines with variation in structure than is found for monoamines; this is largely due to the fact that for these molecules there is no such regular compensation of differences in $\varepsilon_{conj.}$ by the perturbation term $f(y)$.

The conjugation term contributing to differences in ionization constant between a diamine mono-ion and the corresponding monoamine is simply $g(z)$; from eqn. (3) and the listed values of $g(z)$, it follows that

$$pK(\text{monoamine}) - pK(\text{diamine mono-ion}) = -(q_2 - 1)z/2{\cdot}3RT$$

Since q_2 is always $\gg 1$ and z is negative, the monoamine should always have the higher pK. This is so for all systems of this type listed in the Table.

Prototropic Equilibria of Diamine Ions.—For all diamines so far discussed, reference to the monocarbanion isoconjugate with the proton donor of the first ionization has been unambiguous since, in these symmetrical molecules, the ion obtained by addition of a proton to either of the two amino-groups is the same. This is, of course, not always so; amines such as 1 : 6-naphthylenediamine (X) or diphenyline (XI) can accept a proton at either of the two amino-groups to form a different aminium ion in each case. The carbanions isoconjugate with the aminium ions obtained on addition to the 1- and 6-amino-groups of (X) are respectively Nos. 5 and 2 (Table). Where $\varepsilon\beta_1$, $\varepsilon\alpha_1$, $q\beta_1$, $q\alpha_1$ are the

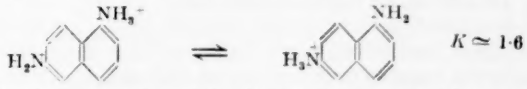
(X)   (XI)

unsaturation energies and extracyclic-carbon atom electron densities of Nos. 5 and 2 the difference in first ionization constant of the two centres is

$$pK(1)_1 - pK(6)_1 = (1/2{\cdot}3RT)[\varepsilon\alpha_1 - \varepsilon\beta_1 + y(q\alpha_1 - q\beta_1)] \simeq -0{\cdot}2$$

Therefore the 6-position is the more basic in (X); the difference of basicity is approximately the difference between that of α- and of β-naphthylamine.

It is noteworthy that since the equilibrium constant for the prototropic reaction

 $K \simeq 1{\cdot}6$

is not far from unity, determination of the dissociation constant by a potentiometric method will yield, not the true value, but a composite constant $K(1)_1K(6)_1/[K(1)_1 + K(6)_1]$. This source of error will generally be appreciable with amines of this type, as the basicities of the two groups are usually not very different.

Proton Dismutation in Diamine–Diaminium Ion Systems.—A further general feature of diamines so far discussed is that in all cases the free energy of the proton dismutation reaction

$$2AH^+ \rightleftharpoons A + AH_2^{++}; \quad \Delta G_D = 2{\cdot}3RT(pK_1 - pK_2)$$

is positive. There is, however, an appreciable variation in this quantity over the range

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Values of $\varepsilon_{conj.}$ (in units of β_{CC}) are calculated from data listed by Wheland (*loc. cit.*), Syrkin and Diatkina (*Acta Physicochem. U.R.S.S.*, 1946, **21**, 23, 641), and Pullman, Berthier, and Pullman (*Bull. Soc. chim.*, 1948, **15**, 540) except where otherwise specified. Charge densities in the dicarbanions (A—O) are listed in the Appendix, p. 691. Dissociation constants were measured in water at the indicated temperature, unless otherwise specified.

[a] Approximate values, from linear plot of $\sqrt{}$self-polarizability (Coulson and Longuet-Higgins, *Proc. Roy. Soc.*, 1948, *A*, **195**, 197) of ring-carbon atom in hydrocarbon residue at point of attachment of extracyclic carbon for aromatic methyl radicals. [b] Estimated value. [c] Unpublished work (with J. L. Morgan). Measurements at ionic strength 0·3. [d] Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469. For consistency with other values quoted, the "P_{ah}" data are used. [e] Kieffer and Rumpf, *Compt. rend.*, 1950, **230**, 1874. [f] Measurements as in *c*. Kolthoff and Bosch, *Rec. Trav. chim.*, 1929, **48**, 37, give pK_1 $6{\cdot}29_{18}$, pK_2 $2{\cdot}80_{18}$. [g] Measurements as in *c*. Clark, Cohen, and Gibbs, U.S. Public Health Reports, 1926, Supp. 54, give pK_1 $4{\cdot}70_{30}$, pK_2 $3{\cdot}48_{30}$. [h] Kuhn and Wassermann, *Helv. Chim. Acta*, 1928, **11**, 3. [i] Kuhn and Zumstein, *Ber.*, 1926, **59**, 488. [j] Kuhn and Wassermann, *Helv. Chim. Acta*, 1928, **11**, 79.

* This and the following pK values were measured in 50% MeOH.

† This and the following values are referred to the H_2O standard, it being assumed that $\Delta pK_1(H_2O \longrightarrow 50\%$ MeOH) has the same value as for 1 : 4-naphthylenediamine (−0·33 unit).

studied. This raises the question of the conditions, if any, under which the free energy of proton dismutation would be negative, in which case pK_1 would be less than pK_2. The possibility of this is brought out by the analogy between this reaction and electronic dismutation among species capable of existence in at least three oxidation states. The formal analogy between these equilibria was first discussed by Michaelis and Schubert (*Chem. Reviews*, 1938, **22**, 437); electronic dismutation is known to occur among the ions formed by oxidation of diamines, and the changes of unsaturation energy on ionization and on oxidation are closely related.

From eqn. (3), and including the statistical term ($\boldsymbol{R}T$ ln 4), the free energy of proton dismutation for any diamine at ~20° should be

$$\Delta G_D = ca.\ \varepsilon_{\text{conj. (2)}} - \varepsilon_{\text{conj. (1)}} + y(q_4 + q_3 - 2q_1) - 2z(q_2 - 1) + 0{\cdot}8 \text{ kcal. mole}^{-1} \quad . \quad (4)$$

where $\varepsilon_{\text{conj. (1)}}$ and $\varepsilon_{\text{conj. (2)}}$ are the conjugation energies of the first and the second CH_2^- group to the hydrocarbon to form the isoconjugate dicarbanion. Equation (4) predicts the general trend of ΔG_D values reasonably well; thus, for the diamines **13**, **9**, **12**, and **14** of the Table, the calculated sequence is 0·7, 1·3, 3·8, and 4·5 kcal. mole^{-1}, and the experimental sequence is ~1·8, 1·5, 4·4, and 4·2 kcal. mole^{-1}. Examination of the data in the Table for other systems shows that, although ΔG_D becomes small as the two amino-groups tend to become independent [*i.e.*, as $\varepsilon_{\text{conj. (1)}}$ approaches $\varepsilon_{\text{conj. (2)}}$], yet it does not become negative, so that the possibility that $pK_2 \gg pK_1$ (at ordinary temperatures) is unlikely.

Non-Coulombic Terms.—No account has so far been taken of integrals of the type $\int \phi_r H' \phi_s^* d\tau (r \neq s) = \delta\beta_{rs}$. If some terms of this kind are non-vanishing in the expansion of the original perturbation expression, eqn. (3) must be modified to:

$$\varepsilon = \varepsilon_{(\mathrm{H})} + \sum_r q_r \delta a_r + 2\Sigma\Sigma_{r<s} p_{rs} \delta\beta_{rs} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where p_{rs} is the mobile order of the rs bond (Coulson and Longuet-Higgins, *loc. cit.*, 1947). The main $\delta\beta$ term that may be important is the difference x between the $\gtrless C{-}NH_2$ (in amine) and $\gtrless C{-}CH_2^-$ (in carbanion) resonance integrals.

We consider first molecules containing only one NH_2 group. The isoconjugate hydrocarbon is a monocarbanion, and it can easily be shown that the mobile order $p_{ex.}$ of the ring-extracyclic bond is the same as in the corresponding radical. Now it is known (*idem*, *Proc. Roy. Soc.*, 1948, *A*, **195**, 188) that for the linking of two unsaturated systems R and S at atoms r and s, $\varepsilon_{\text{conj.}} \simeq p_{rs}$, and this should hold for conjugation of $-\dot{C}H_2$ or $-CH_2^-$ to an aromatic residue. [It has recently been shown by Dewar (*J. Amer. Chem. Soc.*, 1952, **74**, 3341) that in such a case,

$$\varepsilon_{\text{conj.}} \gtrsim p_{rs} \gtrsim \sum_m^{\text{unocc.}} 2 \frac{(a_r^m)^2 \beta_{rs}}{E_m}$$

where a_r^m = coefficient of ϕ_r in $\underset{m}{\Xi}$, the m'th MO of R, of energy E_m.] Strict equality will not be expected; from the limited data available (Jacobs, *J.*, 1952, 292) we may set

$$p_{rs} \simeq 0{\cdot}87\, \varepsilon_{\text{conj.}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

It has been mentioned above that over the range of structure being considered, $\varepsilon_{\text{conj.}}$ varies linearly with $-q_1$; the equation of the line in the figure is

$$\varepsilon_{\text{conj.}} = 1{\cdot}82 - 0{\cdot}7q_1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Combining (5)—(7), we thus have for the energy of conjugation $\varepsilon'_{\text{conj.}}$ of an NH_2 group to an aromatic residue,

$$\varepsilon'_{\text{conj.}} \gtrsim \varepsilon_{\text{conj.}} + 3{\cdot}16\delta\beta + q_1(\delta\alpha - 1{\cdot}2\delta\beta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Equation (8) indicates that if $\delta\beta$ is appreciable compared to $\delta\alpha$, the magnitude of the total perturbation term ($\varepsilon'_{\text{conj.}} - \varepsilon_{\text{conj.}}$) is governed largely by $\delta\beta$; this is in general agreement with the results of Coulson and de Heer (*loc. cit.*; *Trans. Faraday Soc.*, 1951, **47**, 681), derived in a different way.

Even if $\delta\beta$ were large, however (provided that it is not large enough to render the use of perturbation theory invalid), the discussion of the energetics of ionization of monoamines

and diamine mono-ions would require little modification; *e.g.*, for a monoamine, the appropriate modification of eqn. (3) would be

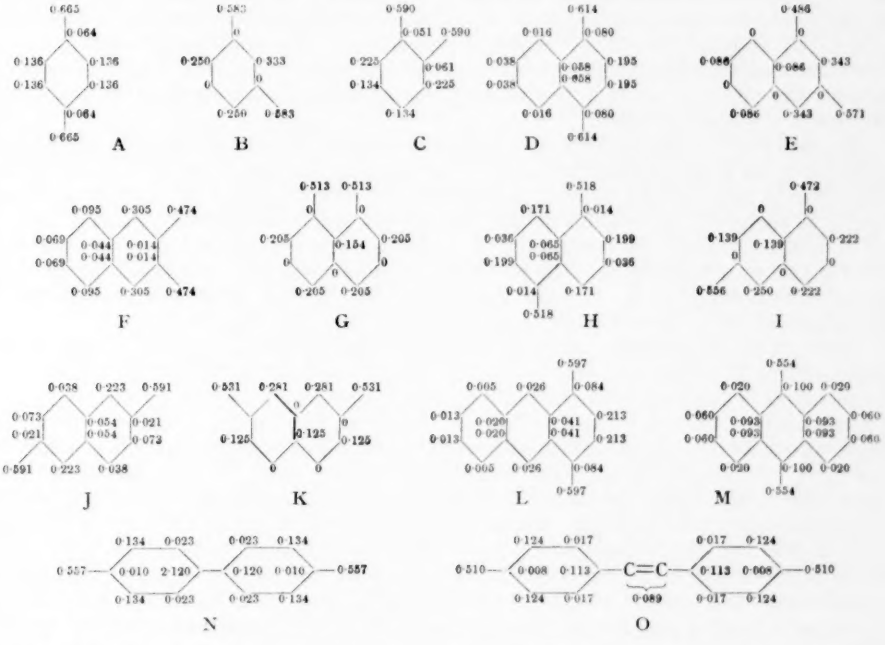
$$2{\cdot}3\boldsymbol{R}T\mathrm{p}K = \varepsilon_{\mathrm{conj.}} + q_1(y - 1{\cdot}2x) - z + (A + 3{\cdot}16x)$$

The only point of difference in the variable terms, which are the ones taken directly into account, is that, whereas the slope, $2{\cdot}3\boldsymbol{R}T\mathrm{p}K - \varepsilon_{\mathrm{conj.}} - \mathrm{g}(z)/q_1$, was formerly interpreted as being equal to y, it must now be set equal to $(y - 1{\cdot}2x)$.

The situation is different for addition of a proton to a diamine, and this permits of an approximate estimate of $\delta\beta$. In this case, a similar treatment, taking into account regularities of extracyclic bond order with structure, yields $(y - 2{\cdot}7x) \simeq -16$ kcal. mole^{-1}. Now it has previously been found that $(y - 1{\cdot}2x) \simeq -13$ kcal. mole^{-1}, and the two numerical values can be regarded as identical within the limits of error of the calculation. This yields the result that $\delta\beta$ is close to zero, *i.e.*, that, to this approximation, the $\gtrless$C–CH_2^- and $\gtrless$C–NH_2 resonance integrals have nearly the same value. As it is fairly certain that the nitrogen AO's are not pure $2p\pi$ functions, it is perhaps understandable that $\delta\beta$ should be small, and this rough calculation indicates that in these systems perturbation terms in $\delta\beta$ can be ignored without introducing serious error.

Electron Densities in Dicarbanions.—In the Appendix, the electron densities in a number of dicarbanions are shown; these have been used in the table. In calculating the distributions for the molecules A, C, D, F, G, L, M, N, and O, the A.O. coefficients listed by Pullman, Berthier, and Pullman (*loc. cit.*) have been employed. Where the dicarbanions contain two non-bonding MO (as also in G), the required orthonormal sets of A.O. coefficients have been obtained from those of two arbitrary sets satisfying the condition $\varepsilon = 0$ by the method of Coulson and Longuet-Higgins (*Phil. Mag.*, 1949, **40**, 1172). The values shown are those of $q_r - 1$ for atom r of a molecule.

Appendix: net π-electron densities in dicarbanions.



The author is indebted to Prof. H. C. Longuet-Higgins for several useful discussions.

THE UNIVERSITY, MANCHESTER. [*Received, July 18th*, 1952.]

139. *Alkaloids of* Daphnandra *Species. Part IV.* Observations on Repanduline.*

By I. R. C. Bick, K. Doebel, W. I. Taylor, and A. R. Todd.

Repanduline, a yellow alkaloid isolated from the bark of several Australian *Daphnandra* species, yields, on oxidation with potassium permanganate, 5 : 4′-dicarboxy-2 : 3-methylenedioxydiphenyl ether (I; R = R′ = CO_2H). It is concluded that the alkaloid belongs to the bisbenzyl*iso*quinoline group.

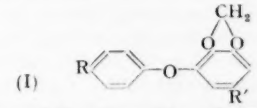
Repanduline was first described by Bick and Whalley (*Univ. Queensland Papers, Dept. Chem.*, 1946, **1**, No. 28) who obtained it, together with repandine, from the bark of *Daphnandra repandula*. Later the same authors isolated it from the bark of *D. Dielsii* (*ibid.*, 1947, **1**, No. 30) and more recently it has also been obtained in this laboratory from the bark of *D. tenuipes* (Part V, following paper). Repanduline is unique among the known *Daphnandra* alkaloids in being yellow, the others being colourless. On the basis of their analytical results Bick and Whalley (*loc. cit.*) suggested for the alkaloid a formula $C_{40}H_{46}O_8N_2$ and considered it to contain two methoxy- and two methylimino-groups. We found considerable difficulty in obtaining consistent analytical data for the alkaloid, owing partly to the tenacious retention of solvent of crystallisation (see Experimental Section) and partly to the overlapping of methoxy- and methylimino-determinations. There is no doubt but that repanduline is a diacid base with a molecular weight in the range 600—650 but, as is frequently the case with alkaloids of the bisbenzyl*iso*quinoline group, it is well-nigh impossible to assign to it a molecular formula on analysis and molecular-weight determinations alone. It would seem that only after some degradation products of lower molecular weight have been isolated and characterised will it be possible to reach finality on the molecular formula of the alkaloid. We quote a formula $C_{37}H_{34}O_7N_2$ with one methoxy- and two methylimino-groups, in reasonable agreement with most of the analytical values, but we emphasise that it is purely provisional. The tendency of repanduline to hold solvent of crystallisation tenaciously may well account for the spread in earlier analytical values; the alkaloid can best be obtained free of solvent by crystallisation from light petroleum or tetrahydrofuran.

Repanduline contains at least one methylenedioxy-group since it gives strong positive reactions in the Labat and Gaebel tests. It is non-phenolic, being insoluble in the Claisen cryptophenol reagent, and, since it is unaffected by cold chromic acid in acetic acid and cannot be acetylated, it contains neither primary nor secondary hydroxyl groups; it does not appear to react with the usual carbonyl reagents. The ultra-violet absorption spectrum (see Fig.) shows a maximum at 2830 Å corresponding in position to that shown by the other *Daphnandra* bases (Part II, *J.*, 1949, 2767; Part III, *J.*, 1950, 1606) and a second broad maximum centred at 3460 Å which in acid solution is displaced to 3260 Å.

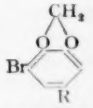
Since all the *Daphnandra* alkaloids so far studied, repandine (Part I, *J.*, 1948, 2170) daphnandrine, daphnoline, aromoline (Part II, *loc. cit.*), and micranthine (Part III, *loc. cit.*), are members of the bisbenzyl*iso*quinoline group of alkaloids it seemed *a priori* likely that repanduline would belong to the same group. However, all attempts to carry out Hofmann degradations on repanduline metho-salts yielded only resins or small amounts of repanduline itself, and Emde degradations were equally unsuccessful. Next, it was found that repanduline with alkaline potassium permanganate gave, in moderate yield, a dicarboxylic acid, repandulinic acid $C_{15}H_{10}O_7$, whose absorption spectrum resembled those of diphenyl ether derivatives (cf. Tomita and Uyeo, *J. Chem. Soc., Japan*, 1943, **64**, 70). On alkali fusion repandulinic acid gave *p*-hydroxybenzoic acid, and decarboxylation furnished a crystalline neutral product which was evidently a diphenyl ether derivative and, like the parent acid, gave a positive reaction for methylenedioxy-groups and contained neither hydroxyl nor methoxyl. From these facts and on biogenetic considerations it seemed probable that repandulinic acid was 5 : 4′-dicarboxy-2 : 3-methylenedioxydiphenyl ether (I; R = R′ = CO_2H) and it was decided to synthesise this compound. Methyl 5-bromo-

* Part III, *J.*, 1950, 1606.

3 : 4-methylenedioxybenzoate (II; R = CO_2Me) was synthesised, by a route essentially similar to that employed independently by Kondo and his co-workers (*Ann. Rep. ITSUU hab. Japan*, 1950, 54; Jap. P. 142,596), from 3 : 4-dihydroxybenzaldehyde by bromination, methylenation with methylene sulphate, and oxidation to the corresponding acid (II; R = CO_2H). Erne and Ramirez (*Helv. Chim. Acta*, 1950, **33**, 912) have used a similar method for the preparation of (II; R = CHO). Fusion of (II; R = CO_2Me) with the potassium salt of methyl *p*-hydroxybenzoate yielded the ester (I; R = R′ = CO_2Me) which was identical with dimethyl repandulinate in m. p., mixed m. p., and infra-red spectrum (Nujol mulls).

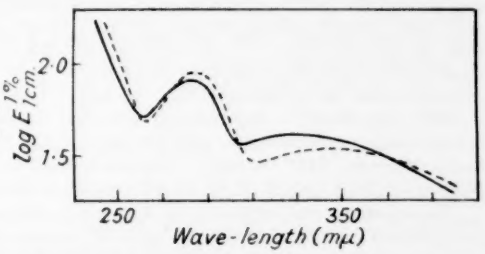


(I)



(II)

The isolation of (I; R = R′ = CO_2H) as an oxidation product coupled with the molecular size of repanduline makes it virtually certain that the latter is an alkaloid of the bisbenzyl*iso*quinoline group. The presence in it of a methylenedioxy-group situated in the diphenyl ether portion of the molecule is, however, unique among the known alkaloids of this group. The only bisbenzyl*iso*quinoline alkaloids known to contain a methylenedioxy-group are cepharanthine (Kondo and Keimatsu, *Ber.*, 1938, **71**, 2553), stephanine (Kondo



Absorption spectrum of repanduline in (– – – –) 95% *ethanol and* (——) 0·1N-*hydrochloric acid.*

and Sanada, *J. Pharm. Soc Japan*, 1927, **47**, 31; 1928, **48**, 163), and some of the minor *Daphnandra* bases (Part V, following paper). Of these, the only one of known structure (cepharanthine) has its methylenedioxy-group in one of the tetrahydro*iso*quinoline residues. As far as we are aware the only related alkaloid in which two hydroxyl (or potential hydroxyl) groups are found in one of the benzyl residues is magnolamine (Proskurnina, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 129; Tomita, Fujita, and Nakamura, *J. Pharm. Soc. Japan*, 1951, **71**, 1075). Interesting as this feature is, there is nothing in the structure of repandulinic acid which would account for the yellow colour of the parent alkaloid.

Repanduline has not the properties of a betaine and its colour is probably associated with some unusual modification of either or both of the tetrahydro*iso*quinoline residues in its molecule; such a view would be in accord with the failure to date of Hofmann and Emde degradation procedures. The number of methylenedioxy-groups in repanduline is not, of course, known, but it seems unlikely that there is more than one. On the assumption that the two (perhaps modified) tetrahydro*iso*quinoline residues are linked by an ethereal oxygen (and there cannot be two such links since repanduline does not give the diphenodioxin colour reactions), five of the seven oxygen atoms in the provisional formula are accounted for in two ether linkages and one methoxy- and one methylenedioxy-group. It seems hardly likely that both the remaining oxygens are present in a second methylenedioxy-group; in view of the yellow colour of the alkaloid some other mode of linkage of at least one of the remaining oxygen atoms is probable.

Experimental

Repanduline.—The isolation procedure used by Bick and Whalley (*loc. cit.*) was modified in that extraction of *D. repandula* bark (4 kg.) was carried out exhaustively with boiling methanol. The extract was evaporated *in vacuo* and the crude alkaloids were dissolved in dilute hydrochloric acid, filtered, and reprecipitated at pH 8 with sodium carbonate. The resultant solid

was extracted with chloroform (Soxhlet). The chloroform extract was concentrated and diluted with ethyl acetate, whereupon crude repanduline (60 g.) crystallised. Final purification could be achieved by recrystallisation or by chromatography in benzene on neutral alumina.

Repanduline crystallises from most of the common organic solvents in slender yellow needles, $[\alpha]_D^{17}$ +473° (*c*, 0·98 in $CHCl_3$), $[\alpha]_D^{16}$ +434° (*c*, 0·2 in MeOH). It shrinks to a dark gum at 180—185° and on further heating decomposes with frothing between 215° and 232°. The following are representative analytical figures obtained on different samples: (i) Recrystallised from methanol. Found, in material dried at room temp./0·1 mm.: C, 69·2, 68·8; H, 5·8, 5·7%; equiv., 324. Found, in material dried at 110°/0·1 mm.: C, 69·6, 69·3; H, 6·0, 5·9; N, 4·4, 4·9; OMe, 5·8, 5·1; NMe, 7·3, 6·0; active H, 0·43%; equiv., 322; *M* (Signer method), 640. Found, in material dried at 140°/0·1 mm.: C, 69·9; H, 6·0; loss on drying, 2·9%. (ii) Recrystallised from light petroleum (b. p. 80—100°). Found, in material dried for 12 hours at 100°/0·1 mm.: C, 72·0; H, 5·9; OMe, 5·6, 5·2; NMe, 9·2, 8·0; active H, 0·07%. (iii) Recrystallised from tetrahydrofuran. Found, in material dried at room temp./0·1 mm.: C, 71·2, 71·2; H, 5·7, 5·8%. (iv) Recrystallised from aqueous 2-ethoxyethanol. Found, in material dried for 12 hours at 120°/0·1 mm.: C, 71·6; H, 5·5%. (v) Recrystallised from *cyclo*hexane. Found, in material dried either at room temp. or at 144°/0·1 mm.: C, 73·0, 73·4; H, 6·9, 6·9%; equiv., 361 [Calc. for $C_{37}H_{34}O_7N_2$ (*M*, 618): C, 71·8; H, 5·5. For $C_{37}H_{34}O_7N_2,H_2O$ (*M*, 636): C, 69·8; H, 5·7. For $C_{37}H_{34}O_7N_2,1{\cdot}5H_2O$ (*M*, 645): C, 68·8; H, 5·8; N, 4·3; OMe 4·8; 2NMe, 9·0; active H, 0·46%. For $C_{37}H_{34}O_7N_2,C_6H_{12}$ (*M*, 702): C, 73·5; H, 6·6%)].

Repanduline was dissolved in a slight excess of warm 5N-hydrochloric acid and set aside. The *dihydrochloride* which separated was recrystallised from water containing a little hydrochloric acid and formed yellow prisms, decomp. slowly at >100° (Found, in material dried for 1 hour at 60°/0·1 mm.: C, 57·9, 57·6; H, 6·2, 6·3; N, 4·0, 3·7; Cl, 10·1%; equiv., 350. $C_{37}H_{34}O_7N_2,2HCl,4H_2O$ requires C, 58·0; H, 5·9; N, 3·7; Cl, 9·5%; equiv., 382. Found, in material dried for 12 hours at 100°/0·1 mm.: C, 61·1, H, 6·2. $C_{37}H_{34}O_7N_2,2HCl,2H_2O$ requires C, 61·1; H, 5·4%). *Repanduline dioxalate* separated from a warm solution of the base in concentrated aqueous oxalic acid and crystallised from aqueous methanol as bright yellow tetrahedra, decomp. 214° (Found, in material dried for 1 hour at 60°/0·1 mm.: C, 56·5; H, 5·2; N, 3·3. $C_{37}H_{34}O_7N_2,2C_2H_2O_4,4H_2O$ requires C, 56·6; H, 5·3; N, 3·2%).

Repanduline was refluxed for 6 hours in benzene with an excess of methyl iodide. The precipitated *dimethiodide* was washed with benzene and recrystallised from methanol in which it was only slightly soluble, forming yellow needles, decomp. 240° (Found, in material dried for 12 hours at 100°/0·1 mm.: C, 48·9; H, 4·8. $C_{39}H_{40}O_7N_2I_2,3H_2O$ requires C, 48·9; H, 4·8%). Light absorption in 95% ethanol: max. at 2850 ($E_{1\,cm.}^{1\%}$, 55) and 3260 Å ($E_{1\,cm.}^{1\%}$, 29·8).

Oxidation of Repanduline.—A solution of repanduline (9·6 g.) in 2N-sulphuric acid (900 c.c.) was neutralised with aqueous potassium hydroxide (4%), then 2% aqueous potassium permanganate (21 c.c. ≡ *ca.* 27 O) was added during 2 hours with vigorous stirring. Manganese dioxide was filtered off and washed with hot water (1 l.) and the combined filtrate and washings were concentrated to 150 c.c. at 40° under reduced pressure. The solution was made acid to Congo-paper and the precipitate filtered off, dissolved in methanol, and treated with excess of ethereal diazomethane. The product (2·41 g.) was chromatographed in benzene on neutral alumina (60 g.), the benzene eluate yielding *dimethyl repandulinate* (444 mg.) as colourless needles. Recrystallised from methanol this had m. p. 116—118°, and gave a positive test for methylenedioxy-groups with the Labat reagent (Found, in sublimed material: C, 61·9; H, 4·3; MeO, 20·4, 19·5. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·3; 2MeO, 19·0%). Light absorption in 95% ethanol: max. at 2540—2560 Å (log ε 4·42). Hydrolysis of the diester with methanolic potassium hydroxide (10%) yielded *repandulinic acid*, colourless needles (from methanol), m. p. 290° (decomp.) (Found: C, 60·1; H, 3·5. $C_{15}H_{10}O_7$ requires C, 59·6; H, 3·3%).

Potash Fusion of Repandulinic Acid.—Repandulinic acid (50 mg.) and zinc dust (25 mg.) were added to potassium hydroxide (1 g.) at 240° and the temperature of the melt raised to 325° during 10 minutes. After a further 12 minutes at this temperature the melt was cooled, triturated with dilute hydrochloric acid, then extracted with ether, leaving a crystalline acidic residue (30 mg.). The latter on methylation with ethereal diazomethane afforded an ester, m. p. 44—45° undepressed in admixture with an authentic sample of methyl *p*-methoxybenzoate (m. p. 44—45°).

Methyl 5-Bromo-3: 4-methylenedioxybenzoate.—This was prepared by essentially the method used by Kondo and his co-workers (*loc. cit.*); recrystallised from methanol it had m. p. 96° (lit., m. p. 96°).

5: 4′-Dicarbomethoxy-2: 3-methylenedioxydiphenyl Ether (Dimethyl Repandulinate).—Methyl

p-hydroxybenzoate (1·54 g.) was added to a solution of potassium (0·39 g.) in methanol (10 c.c.) and evaporated to dryness. The residue was then mixed with methyl 5-bromo-3 : 4-methylenedioxybenzoate (5·21 g.) and copper powder (0·3 g.) and heated at 200° during 5 hours. The cooled melt was extracted with ether, and the extract washed with dilute sodium hydroxide, then water, and dried (Na_2SO_4). The solution was evaporated to dryness and the methyl piperonylate and methyl 5-bromopiperonylate were sublimed off at 100°/10 mm. The residue was dissolved in benzene and filtered through activated alumina (20 g.) which was washed with benzene. The crude ester obtained by evaporation of the filtrate was purified by recrystallisation from methanol, giving 5 : 4′-*dicarbomethoxy*-2 : 3-*methylenedioxydiphenyl ether* (240 mg.), m. p. 119—120° (Found : C, 61·6; H, 3·9%).

Hydrolysis of the ester afforded synthetic 5 : 4′-dicarboxy-2 : 3-methylenedioxydiphenyl ether, m. p. 290° (decomp.) (from methanol) alone or mixed with repandulinic acid.

2 : 3-*Methylenedioxydiphenyl Ether.*—A mixture of 5 : 4′-dicarboxy-2 : 3-methylenedioxydiphenyl ether (78 mg.) and copper powder (160 mg.) in quinoline (3 c.c.) was refluxed for 30 minutes. The cooled mixture was diluted with ether and filtered, and the solution washed thoroughly with hydrochloric acid (2N), then sodium hydrogen carbonate, and finally water, dried, and evaporated. The residue of crude 2 : 3-*methylenedioxydiphenyl ether* (54 mg.) was sublimed at 80°/12 mm. and then recrystallised from ethanol, giving colourless plates, m. p. 51—52° (Found : C, 73·1, 72·9, 73·3; H, 5·0, 5·1, 5·2. $C_{13}H_{10}O_3$ requires C, 72·9; H, 4·7%). Light absorption in 95% ethanol : max. at 2760 (log ε 3·46) and 2700 Å (log ε 3·44). The substance gave no depression in m. p. when mixed with the decarboxylation product (m. p. 51—52°) of repandulinic acid.

Our thanks are due to the Swiss " Stiftung für Stipendien auf dem Gebiete der Chemie " for a grant to one of us (K. D.), to the Australian National University for a scholarship (to I. R. C. B.) and to the University of Cambridge for an I.C.I. Fellowship (to W.I.T.).

University Chemical Laboratory, Cambridge. [*Received, October* 21*st*, 1952.]

140. *Alkaloids of* Daphnandra *Species. Part V.* An Examination of the Alkaloidal Content of* D. micrantha *and of* D. tenuipes. *Isolation of Some Minor* Daphnandra *Alkaloids.*

By I. R. C. Bick, W. I. Taylor, and A. R. Todd.

The alkaloidal content of the bark of *D. micrantha* collected in various localities and at different times varies considerably. Samples from Queensland contained mainly micranthine, but daphnoline and daphnandrine were also found in barks from New South Wales. The bark of *D. tenuipes*, a species found in northern New South Wales, yielded repanduline, aromoline, and a new alkaloid tenuipine; the leaves yielded a de-*N*-methyltenuipine. An examination of *D. repandula* for minor alkaloids led to the isolation of *O*-methylrepandine and repandinine, probably identical with (±)-tenuipine; *D. dielsii* similarly examined yielded *O*-methylrepandine, repandinine, and tenuipine. The structure of the new alkaloids is discussed.

In his work on *Daphnandra micrantha*, Pyman (*J.*, 1914, **105**, 1679) isolated from the bark of this Australian tree three alkaloids, daphnandrine, daphnoline, and micranthine. As recorded earlier (Bick, Ewen, and Todd, *J.*, 1949, 2767; Bick and Todd, *J.*, 1950, 1606) we were unable to detect any alkaloid other than micranthine in samples of *D. micrantha* bark collected in Southern Queensland. This might mean that the material examined by Pyman was wrongly identified or that the alkaloid content of the species varied according to the locality in which it was grown, the size of the tree, or the season in which the bark was collected. To clarify the position we have now examined samples of *D. micrantha* collected at various times, not only in Queensland but also in northern New South Wales. Pyman's material was supplied to him by the Director of the Sydney Botanic Gardens, and presumably was collected in New South Wales, although unfortunately there appears to be no record of the transaction either in this country or in Australia. Our results are shown in the annexed Table

* Part IV, preceding paper.

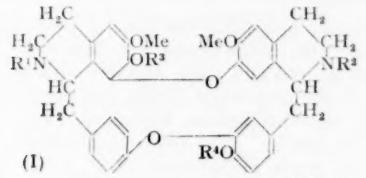
Locality	Size of tree	Date collected	Alkaloids
Mt. Glorious, Queensland (bark)	Stem diam. 3′ at breast height	March, 1945	Micranthine
,, ,, ,, ...	80′ × 2′	April, 1946	Micranthine
Upper Brookfield, Queensland (wood)...	15—20′ × 2—4″	April, 1946	Micranthine
Draper's crossing, near Brisbane (bark)	25—30′ × 3—4″	January, 1948	Micranthine
Upper Brookfield (bark)	35′ × 5″	August, 1949	Micranthine, daphnoline
Wauchope, N.S.W. (bark)	Stem diam. 14″	September, 1949	Micranthine, daphnoline, daphnandrine
Toonumbar State Forest, N.S.W. (bark)	75′ × 16″	December, 1950	Micranthine, daphnandrine

It is noteworthy that bark obtained from Wauchope on the New South Wales coast some 200 miles north of Sydney contained daphnandrine, daphnoline, and micranthine, although the relative proportions differed from those found by Pyman (*loc. cit.*), and that material collected in the Toonumbar State Forest, N.S.W., just 25 miles south of the Queensland border, contained daphnandrine and micranthine. Micranthine seems to be the dominant alkaloid in the more northerly specimens, and was indeed the only one isolated from most of the Queensland material; that even there it may have been accompanied by traces of daphnoline cannot be wholly excluded, since in some of our earliest examinations the technique employed might not have revealed minute amounts of this alkaloid. In all our later work separation of the individual alkaloids has been carried out as far as possible by chromatography on neutral alumina, and their identification by comparison with authentic specimens. From our results it seems probable that the material examined by Pyman (*loc. cit.*) was in fact *D. micrantha*, and that the alkaloidal content of this species varies according to the locality in which the tree is grown; there is no evidence from the admittedly small number of samples we have studied that there is any very marked variation according to age or season.

In previous papers degradative evidence has been given for the structures of repandine (Bick and Todd, *J.*, 1948, 2170), daphnandrine, daphnoline, aromoline (Bick, Ewen, and Todd, *loc. cit.*) and micranthine (Bick and Todd, *J.*, 1950, 1606). The first four all belong to the oxyacanthine series of bisbenzyl*iso*quinoline alkaloids, but it was not known which of the structures (I; $R^1 = R^2 = R^3 = Me$, $R^4 = H$) and (II) represented oxyacanthine and which berbamine. This ambiguity has now been removed by the elegant work of Tomita, Fujita, and Murai (*J. Pharm. Soc. Japan*, 1951, **71**, 226) who by degradation of *iso*tetrandrine with metallic sodium in liquid ammonia have established that berbamine is (II) and hence that oxyacanthine is (I; $R^1 = R^2 = R^3 = Me$, $R^4 = H$). Repandine, a diastereoisomer of oxyacanthine, is therefore (I; $R^1 = R^2 = R^3 = Me$, $R^4 = H$), daphnandrine is (I; $R^1 = Me$ and $R^2 = H$ or *vice versa*, $R^3 = H$, $R^4 = Me$), daphnoline (I; $R^1 = H$, $R^2 = Me$ or *vice versa*, $R^3 = R^4 = H$), and aromoline (I; $R^1 = R^2 = Me$; $R^3 = R^4 = H$). The structure assigned to micranthine (III; R^1 or R^2, and R^3 or $R^4 = Me$; others = H) (*J.*, 1950, 1606) remains as before uncertain only as regards the precise distribution of methyl groups. Since our earlier report (Bick, Ewen, and Todd, *loc. cit.*) we have been able, through the kindness of Dr. H. Kondo, to compare purified specimens of trilobamine directly with daphnoline by m. p., mixed m. p., and *X*-ray powder photography, and have fully confirmed our view that these two substances are identical.

Following our examination of *D. micrantha* barks from various sources we re-examined the barks of *D. repandula* and *D. dielsii* for alkaloid content, using our improved methods of extraction and chromatographic analysis to supplement the original studies of Bick and Whalley (*Univ. Queensland Papers, Dept. Chem.*, 1946, **1**, No. 28; 1947, **1**, No. 30; 1948, **1**, No. 33) and to extend our studies to another as yet unexamined *Daphnandra* species, *D. tenuipes*. From *D. repandula* bark we have now isolated, in addition to the repandine and repanduline reported by Bick and Whalley (*loc. cit.*, No. 28), two new minor alkaloids in very small amount. One of these, a colourless base $C_{38}H_{42}O_6N_2$, has been identified as *O*-methylrepandine by showing that its dimethiodide is identical with *O*-methylrepandine dimethiodide (Bick and Todd, *J.*, 1948, 2170). The second alkaloid, for which we propose the name repandinine, gives analytical values corresponding to $C_{38}H_{40}O_7N_2$. It gives a positive reaction for methylenedioxy-groups, is colourless, contains 3 methoxy- and 2 methylimino-groups, and is non-phenolic. Repandinine has zero optical rotation

in chloroform and in 0·1N-hydrochloric acid for either the sodium or the mercury line, which suggests that it is a racemic compound or that it is internally compensated. The infra-red spectrum of repandinine in chloroform solution is identical with that of tenuipine (see below) so that it is highly probable that it is the racemic form of tenuipine. Because of the small



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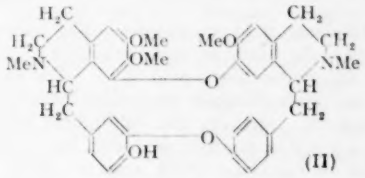

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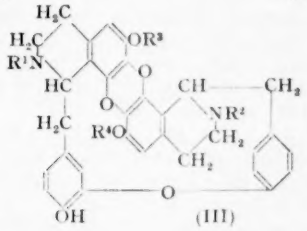

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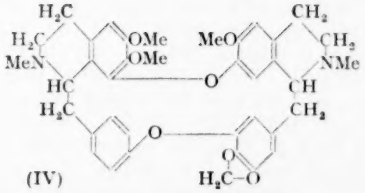

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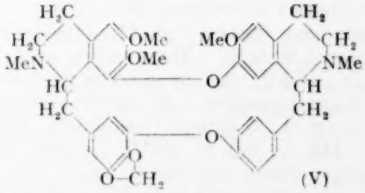

(V)

amount of material available we have not been able to confirm the identity by exhaustive methylation.

Re-examination of the bark of *D. dielsii*, reported by Bick and Whalley (*loc. cit.*, No. 30) to contain only repanduline, has shown that it contains in addition small amounts of *O*-methylrepandine, repandinine, and tenuipine identical with a new alkaloid obtained from *D. tenuipes*.

D. tenuipes is a distinct *Daphnandra* species which occurs in the Tweed River and Doyle's River districts of northern New South Wales, where *D. micrantha* apparently is not found; it is a common tree in the Whian Whian State Forest near Lismore, New South Wales. We are indebted for this information to Dr. L. J. Webb who also provided a sample of the bark for investigation. From it we isolated repanduline as the main alkaloidal constituent together with a very small amount of aromoline (I; $R^1 = R^2 = Me$, $R^3 = R^4 = H$), and somewhat larger amounts of a colourless alkaloid which we name tenuipine. Tenuipine has a formula $C_{38}H_{40}O_7N_2$ and contains 3 methoxy- and 2 methylimino-groups. It has no phenolic properties, but gives positive reactions for a methylenedioxy-group. Its molecular formula and occurrence in a *Daphnandra* species make it almost certain that tenuipine is a bisbenzyl*iso*quinoline alkaloid and if, as is a reasonable assumption, it bears the methylenedioxy-group in the same position as in the accompanying repanduline (Bick, Doebel, Taylor, and Todd, *loc. cit.*) it has a probable structure (IV) or (V). From the leaves of *D. tenuipes* we have isolated in small yield a single colourless base, $C_{37}H_{38}O_7N_2$, which has no phenolic properties but gives a positive reaction for a secondary amino-group, the presence of which can also be inferred from its infra-red absorption spectrum. Methylation with methyl iodide in methanol affords tenuipine dimethiodide, identified by m. p., mixed m. p., optical rotation, *X*-ray powder photographs, and infra-red absorption spectrum. We therefore conclude that this new alkaloid is a de-*N*-methyltenuipine. De-*N*-methyltenuipine shows only two methoxy-groups in the Zeisel estimation, the third appearing as an apparent

methylimino-group in the *N*-methyl determination. Determination of methoxy- and methylimino-groups in the *Daphnandra* alkaloids by standard methods is difficult; the results frequently vary and are in general rather unreliable.

Experimental

Alkaloids of D. micrantha.—The following example illustrates the general procedure employed: the finely ground bark (250 g.) from Toonumbar State Forest was shaken for 4 days with 5% hydrochloric acid (2 l.). The extract was filtered and made alkaline with ammonia, and the crude alkaloids were centrifuged off, washed well with water, dried, and extracted with chloroform. Shaking the chloroform extract with aqueous sodium hydroxide (5%) yielded only a trace of phenolic material, too small to be worked up. The crude alkaloids (8 g.), dissolved in methanol–ethyl acetate, slowly deposited crude micranthine (4·5 g.), m. p. 188° (decomp.). This (1·5 g.) was chromatographed in chloroform on neutral alumina (*ca.* 100 g.). The chloroform eluate (1·5 l.) gave daphnandrine (330 mg.), which after recrystallisation from methanol had m. p. 270° (decomp.), $[\alpha]_D^{16}$ +480° (*c*, 1·2 in $CHCl_3$, on a dried sample). Further elution with chloroform containing methanol (2%) yielded micranthine; recrystallised from methanol it had m. p. 190—194° (decomp.), $[\alpha]_D^{16}$ −221° (*c*, 1·3 in $CHCl_3$, on a dried sample) (Found: C, 72·0; H, 6·0; N, 5·3. Calc. for $C_{34}H_{32}O_6N_2$: C, 72·3; H, 5·7; N, 5·0%).

Alkaloids of D. repandula.—Finely powdered bark (4 kg.) was exhaustively extracted with boiling methanol until the extract gave a negative reaction with Meyer's reagent. The dark brown extract was evaporated to dryness *in vacuo* at 40°. The bases were taken up in hydrochloric acid (1·5%; 5 l.), filtered, and reprecipitated at pH 8 with sodium carbonate. The crude product so obtained (370 g.) was extracted (Soxhlet) with chloroform in 60-g. lots, the extracts were washed with 3% aqueous sodium hydroxide, then water, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting solid was dissolved in ethanol (500 c.c.), and ethyl acetate (300 c.c.) added, whereupon crude repanduline crystallised. The crude base (60 g.) in benzene was chromatographed over neutral alumina (1800 g.), to yield from the benzene and benzene–chloroform (1 : 1) eluates repanduline (34·9 g.), decomp. 180°, $[\alpha]_D^{17·5}$ +473° (*c*, 0·98 in $CHCl_3$), $[\alpha]_D^{16}$ +434° (*c*, 0·19 in MeOH). Crude repanduline (24·9 g.) from the mother-liquors of the extraction above was taken up in 0·1% hydrochloric acid and a solution of ammonium reineckate added until there was no further precipitate. The dried precipitate in acetone (2 l.) was poured on activated alumina which by elution with acetone gave a colourless crystalline solid (0·8 g.), followed by a yellow solution which yielded repanduline (0·9 g.), $[\alpha]_D^{14}$ +469° (*c*, 1·2 in $CHCl_3$), and finally a reineckate which contained repanduline (12 g.). The crystalline solid was chromatographed in benzene–chloroform (1 : 1) on neutral alumina; the benzene–chloroform (1 : 1) eluate afforded repandinine (0·4 g.) and on further elution with chloroform–methanol (1 : 1) *O*-methylrepandine (*ca.* 0·2 g.).

Repandinine.—Crystallised from acetone–methanol *repandinine* formed fine needles, m. p. 243°, $[\alpha]_D^{15}$ ±0·0° (*c*, 0·25 in $CHCl_3$ or 1·0 in 0·1N-hydrochloric acid) [Found: C, 71·6, 71·6; H, 6·5, 6·3; N, 4·4; MeO, 13·1; MeN, 7·5, 10·0; *M* (Rast), 533. $C_{38}H_{40}O_7N_2$ requires C, 71·7; H, 6·3; N, 4·4; 3MeO, 14·6; 2MeN, 9·1%; *M*, 637]. It gave a pink colour with concentrated sulphuric acid and a positive test for a methylenedioxy-group with Gaebel's and Labat's reagents. There was no reaction with either ferric chloride or Millon's reagent.

Repandinine (100 mg.) was refluxed in methanol for 20 minutes with excess of methyl iodide, the solution evaporated to dryness, and the *dimethiodide* recrystallised from water as colourless needles, decomp. 275°, $[\alpha]_D^{15}$ ±0·0° (*c*, 0·4 in 50% aqueous EtOH) (Found, in air-dried material: C, 50·5; H, 5·8. $C_{40}H_{46}O_7N_2I_2,2H_2O$ requires C, 50·3; H, 5·3%).

O-*Methylrepandine* crystallised in needles (from methanol), m. p. 211°, $[\alpha]_D^{13}$ −73° (*c*, 0·3 in $CHCl_3$), $[\alpha]_D^{20}$ −108° (*c*, 1·7 in 0·1N-hydrochloric acid) (Found: C, 73·7; H, 7·0; N, 4·3; MeO, 18·1; MeN, 9·7. $C_{38}H_{42}O_6N_2$ requires C, 73·4; H, 6·8; N, 4·5; 4MeO, 19·9; 2MeN, 9·3%).

O-Methylrepandine (50 mg.) was refluxed in methanol with methyl iodide to yield the dimethiodide, colourless needles (from water), decomp. 255—260°, $[\alpha]_D^{20}$ −93° (*c*, 1·6 in 50% aqueous EtOH) (Found: C, 50·5; H, 5·8; I, 26·6; loss at 110°/0·1 mm., 4·8. Calc. for $C_{40}H_{48}O_6N_2I_2,2·5H_2O$: C, 50·5; H, 5·6; I, 26·6; H_2O, 4·7%). It gave a Debye–Scherrer diagram identical with *O*-methylrepandine dimethiodide ($[\alpha]_D^{15}$ −95°) described by Bick and Todd (*J.*, 1948, 2170).

Alkaloids of D. tenuipes.—Finely ground bark (770 g.) was shaken at room temperature with successive quantities of aqueous tartaric acid (0·25%) until Meyer's reagent gave only a faint reaction. The combined extracts (25 l.) were concentrated *in vacuo* at 40° to 1·5 l. and made

alkaline with ammonia, and the precipitate was dried *in vacuo* (P_2O_5). The dry powdered solid (53 g.) was extracted with chloroform and the extract shaken with aqueous sodium hydroxide. The aqueous layer containing aromoline was separated and the chloroform layer washed, dried, and evaporated. The residue was redissolved in benzene and chromatographed on neutral alumina. On elution with benzene–chloroform (1 : 1) a colourless fraction was obtained which on crystallisation from acetone–methanol yielded *tenuipine* (0·2 g.). Further elution with benzene–chloroform (1 : 1) gave repanduline (5 g.), $[\alpha]_D^{20}$ +459° (*c*, 1·2 in $CHCl_3$).

Tenuipine. Recrystallised from acetone–methanol or methanol the alkaloid formed colourless prisms, m. p. 140—145° $[\alpha]_D^{20}$ −258° (*c*, 2·8 in $CHCl_3$) [Found : C, 71·6, 71·0; H, 6·7, 6·2; N, 4·7; MeO, 12·9; MeN, 7·7; *M* (Rast), 545. $C_{38}H_{40}O_7N_2$ requires C, 71·7; H, 6·3; N, 4·4; 3MeO, 14·6; 2MeN, 9·1%; *M*, 637]. It gave a positive reaction for a methylenedioxy-group with Gaebel's and Labat's reagents. Tests for a phenolic group with ferric chloride, Millon's reagent, and Claisen's cryptophenol reagent were negative.

Tenuipine (100 mg.) was refluxed in methanol with methyl iodide for 20 minutes. The solvent was removed *in vacuo* and the *dimethiodide* recrystallised from 50% aqueous ethanol as colourless prisms, m. p. 267—272° (decomp.), $[\alpha]_D^{15}$ −165° (*c*, 1·0 in 50% aqueous EtOH) (Found, in material dried *in vacuo* at room temperature : C, 49·1; H, 5·7. $C_{40}H_{46}O_7N_2I_2,3H_2O$ requires C, 49·3; H, 5·4%).

Aromoline. The sodium hydroxide extract (*ca.* 1 l.) obtained above was diluted with water (3 l.) and acidified with dilute hydrochloric acid. A flocculent precipitate was removed, the solution neutralised wtih sodium carbonate, and the precipitated base (1·5 g.) filtered off, dried, and extracted with chloroform. After concentration crystals of aromoline (50 mg.) separated during some days; they had m. p. 175° undepressed in admixture with an authentic sample of aromoline isolated from *D. aromatica* (Bick and Whalley, *loc. cit.*, No. 33).

Alkaloid from the Leaves of D. tenuipes (*De-N-methyltenuipine*).—The finely ground leaves (2 kg.) were stirred with hydrochloric acid (5%; 3·5 l.) for 24 hours, the mixture was filtered, and the residue triturated with water for a further 24 hours. This washing with water was repeated four times in all, and the combined extracts were concentrated *in vacuo* to *ca.* 1 l. and brought to pH 7·5 with ammonia, and the resulting alkaloid was filtered off, washed well with water, and dried. The crude base (1 g.), obtained as a faintly yellow powder after extraction with chloroform (Soxhlet), crystallised from 95% ethanol or chloroform–methanol in needles, m. p. 211° (decomp.), $[\alpha]_D^{12}$ −218° (*c*, 0·8 in $CHCl_3$). *De-N-methyltenuipine* was insoluble in the Claisen cryptophenol reagent, gave a positive Labat test for a methylenedioxy-group, and afforded a red colour followed by a green precipitate on treatment with sodium nitrite in dilute acetic acid solution (Found : C, 71·1; H, 6·1; MeO, 9·6, 10·3; MeN, 7·3, 7·9. $C_{37}H_{38}O_7N_2$ requires C, 71·3; H, 6·2; 2MeO, 10·0; 2MeN, 9·4%). Light absorption in 95% ethanol; max. at 2820 (ε 7200) and 2110 Å (ε 84,800).

The base (90 mg.) was refluxed in methanol with methyl iodide for 2 hours. Addition of water to the resulting solution yielded flat plates of the dimethiodide, m. p. 261—265° (decomp.), $[\alpha]_D^{15}$ −154° (*c*, 0·4 in 50% aqueous EtOH), identical in infra-red absorption spectrum (Nujol mull) and *X*-ray powder photograph, with tenuipine dimethiodide in admixture with which it gave no depression in m. p. (Found : C, 49·3; H, 5·4%).

Alkaloids of D. dielsii.—A portion (*ca.* 250 c.c.) of a stock methanolic extract of *D. dielsii* bark remaining from earlier work was used in seeking for minor alkaloids. The extract was evaporated to dryness under reduced pressure, and the residue (*ca.* 120 g.) was then extracted with cold dilute hydrochloric acid, which left behind much non-basic material. The extract was made alkaline with ammonia, the precipitate collected, dried and extracted with chloroform, and the chloroform extract concentrated to small bulk. On addition of methanol the crude alkaloid (8 g.), consisting largely of repanduline, separated; it was dissolved in benzene and put on a column of neutral alumina. Elution with benzene gave pure repanduline, m. p. 183° (decomp.), $[\alpha]_D^{15}$ +490° (*c*, 1·01 in $CHCl_3$). After elution of the repanduline, the column was washed with methanol, and the washings were combined with the mother-liquor from the separation of the above crude alkaloid and evaporated. The residue so obtained was dissolved in benzene, the solution filtered through neutral alumina (1·5 kg.), and the filter washed thoroughly with benzene; the filtrate and washings yielded a further amount of repanduline (2 g.). The alumina was then washed with benzene–methanol (50 : 1), which eluted the remainder of the alkaloids, leaving behind highly coloured impurities. The eluted product was separated roughly into three fractions according to its solubility in methanol. (*a*) Soluble fraction. This material was separated into two fractions of greater and lesser solubility in light petroleum (b. p. 80—100°). From the former small amounts of repanduline, repandinine,

and tenuipine were obtained by fractional crystallisation from methanol, and from the less soluble fraction, tenuipine, repanduline, and *O*-methylrepandine were obtained by chromatography on neutral alumina in benzene. (*b*) Moderately soluble fraction, almost wholly crude repanduline ($[\alpha]_D^{15} = +360°$). (*c*) Insoluble fraction. This gave repandinine and *O*-methyl repandinine on chromatography in benzene.

Details of the minor alkaloids isolated are:

Repandinine. Total yield *ca.* 150 mg.; m. p. 240—242°, $[\alpha]_D^{14} \pm 0°$. A mixed m. p. with repandinine isolated from *D. repandula* showed no depression.

O-*Methylrepandine.* Total yield *ca.* 100 mg.; m. p. and mixed m. p. 212°, $[\alpha]_D^{15} -70·5°$, (*c*, 1·02 in $CHCl_3$) (Found: C, 73·3; H, 7·1. Calc. for $C_{38}H_{42}O_6N_2$: C, 73·4; H, 6·8%).

Tenuipine. Total yield *ca.* 300 mg. Tenuipine is dimorphous and can be obtained in two interconvertible forms, prisms, m. p. 140°, and needles, m. p. 170°, both from methanol. The alkaloid had $[\alpha]_D^{16} -250°$ (*c*, 0·75 in $CHCl_3$) (Found, in material dried at 100°/0·1 mm. for 12 hours: C, 71·2; H, 6·3; N, 4·3; MeO, 13·0; MeN, 8·1%). Light absorption in 95% ethanol: max. at 2820 Å (ε 6560).

We acknowledge gratefully the co-operation of Mr. L. J. Webb of C.S.I.R.O., Queensland, who supplied the plant material. One of us (I. R. C. B.) participated in this work during tenure of an Australian National University scholarship, and another (W. I. T.) during tenure of an Imperial Chemical Industries Fellowship.

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141. *The Reaction of Diazonium Salts with Amines.*

By S. KRUGER.

The relative reactivity of a number of monosubstituted anilines was measured, two aromatic amines being allowed to compete for a limited amount of diazonium salt and the relative amounts of diazoamino-compound formed being measured. The results are discussed in the light of electronic theory.

MOST work on the effect of substituents on the reactivity of the benzene ring has been concerned with direct substitution on one of the carbon atoms of the ring, usually by bromine or the nitro-group. The present investigation is designed to show that, under certain conditions, a suitable reagent can be caused to attack a side chain attached to the aromatic system without quantitatively altering the results to be expected for direct substitution from a consideration of various polarization and polarizability effects.

The reaction chosen was that between aromatic amines and diazonium salts, leading mainly to diazoamino-compounds. The method was to allow a mixture of one equiv. of each of two aromatic amines to react with one equiv. of diazonium salt and to determine the proportions of the two possible diazoamino-compounds formed. As one of the amines chosen contained a halogen substituent, the molar ratio (R) of the two diazoamino-compounds could be readily determined by analysis.

The ratio of the velocity constants of the two reactions can then be calculated as follows: Let one mole of each of two amines react with one mole of diazonium salt. Then at time t, y moles of one and z moles of the other amine will have reacted. Hence $dy/dt = k_1(1-y)(1-x)$ and $dz/dt = k_2(1-z)(1-x)$, where x is the amount of diazonium salt which has reacted. Hence, $k_2\int dy/(1-y) = k_1\int dz/(1-z)$ or $k_1/k_2 = \log_e(1-y)/\log_e(1-z)$. When reaction is complete all the diazonium salt will have reacted, hence $y + z = 1$, and as $R = y/z = y/(1-y)$, substitution leads to $k_1/k_2 = [\log_{10} 1/(R+1)]/[\log_{10} R/(R+1)]$.

The values thus obtained could not be correlated with known physical constants (such as dipole moments or pK values), but a reasonable correlation was established with Sutton's $\mu_{al.} - \mu_{ar.}$ values (*Proc. Roy. Soc.*, 1931, *A*, **133**, 668), which give a measure of the ability of the substituents to attract or repel electrons and are consequently related to the directing power of such groups. With one exception the reaction velocity was high for positive and low for negative value of this constant (see Table 1). Hence, the coupling reaction behaves as if it were essentially a nuclear electrophilic reaction, and such a reaction could not involve

the aminium ion where the nuclear electron density has been decreased to an extremely low level by the positive charge on the nitrogen atom. Wistar and Bartlett (*J. Amer. Chem. Soc.*, 1941, **63**, 413) reached a similar conclusion from other evidence.

Experimental

The competitive coupling experiments were carried out as follows: 0·01 mole of each of the two amines in methanol (40 ml.) was cooled to 2°, and 0·01 mole of solid phenyldiazonium sulphate (or nitrate), in 20 ml. of ice-cold water, was added. The mixture was stirred for 30 minutes at constant temperature. The yellow precipitate was filtered off, washed with *ca.* 700 ml. of cold water, and dried at room temperature *in vacuo* (P_2O_5). With *o*-chloroaniline naphthalene-β-diazonium sulphate was used instead of the benzenediazonium sulphate, as the latter gave a liquid diazoamino-compound. In some experiments 0·02 mole of sodium hydrogen carbonate was added to the reaction mixture, but made no significant difference. The solubility of the products in the mixture was not such as to affect the results except for 2-bromodiazoaminobenzene, which was particularly soluble. Products from experiments involving *m*-iodoaniline tended to resinify when washed. This was avoided by washing the product with 15 ml. of ice-cold ligroin and then with water containing 0·5% of ammonia.

The values given are averages of 5—10 determinations, but reproducibility was sometimes no better than about ±20% in spite of rigid adherence to the standard conditions. The discrepancies are principally due to the instability of the diazonium salt and occasional resinification. As can be seen, however, the differences between the compounds listed are so large that the order of reactivities is undoubtedly significant.

The pure diazoaminobenzenes were prepared as follows: 0·1 mole of the substituted aromatic amine was dissolved in 20 ml. of methanol (or sufficient to hold all the amine in solution after addition of the aqueous diazonium salt solution); 0·1 mole of aniline was diazotized in the usual manner, neutralized with excess of sodium hydrogen carbonate, and slowly added to the stirred amine solution at 4—6°. After 3 hours the precipitate was collected and recrystallized. When *m*-anisidine was thus coupled with diazotized aniline only the aminoazo-compound was formed. The liquid 2-chlorodiazoaminobenzene was characterized by condensation with phenyl *iso*cyanate (see p. 702).

The required fluoroanilines were prepared by the following method: The nitroaniline (0·1 mole) was diazotized and the filtered solution added to morpholine (0·1 mole) in water (200 ml.) containing sodium carbonate (30 g.). A yellow precipitate was rapidly formed, which was filtered off and recrystallized from ethanol (yields quantitative). The phenylazomorpholine was refluxed in a lead vessel for two hours with excess of 48% hydrofluoric acid, neutralized, and extracted with ether. The extract was washed with dilute acid, dried, and distilled *in vacuo*. The fluoronitrobenzenes (yields 30—45%) were reduced to the corresponding anilines.

These *diazoaminobenzenes* which are tabulated were recrystallized from ligroin except where otherwise stated.

Diazoamino-benzene	Form	M. p.	Formula	Found, %			Required, %		
				C	H	N	C	H	N
3-Fluoro-	Yellow needles	90°	$C_{12}H_{10}N_3F$	67·0	4·3	20·1	67·0	4·6	19·5
4-Fluoro-	Yellow prisms	83	,,	66·9	5·0	19·4	,,	,,	,,
3-Cyano-	Yellow needles *	137	$C_{13}H_{10}N_4$	69·7	4·5	25·2	70·3	4·5	25·2
4-Cyano-	,,	150	,,	69·9	4·5	25·1	,,	,,	,,
2-Methoxy-	Small, yellow-brown prisms †	41	$C_{13}H_{13}ON_3$	68·2	5·6	18·2	68·7	5·7	18·5 ‡
4-Methoxy-	Yellow needles	87·5	,,	68·3	5·8	18·3	,,	,,	,, §
2-Bromo-	Yellow-brown needles	67·5	$C_{12}H_{10}N_3Br$	51·7	3·4	15·6	52·2	3·6	15·2 ‖
2-Iodo-	Yellow-brown prisms	108	$C_{12}H_{10}N_3I$	44·3	3·1	13·0	44·6	3·1	13·0 ¶
3-Iodo-	Yellow plates	93	,,	44·3	3·2	13·0	,,	,,	,, **
3-Chloro-	Bunched, yellow needles	87	$C_{12}H_{10}N_3Cl$	62·2	4·3	18·1	62·2	4·4	18·1 ††
3-Acetyl	Yellow, hexagonal plates	105	$C_{14}H_{13}ON_3$	69·9	5·5	17·4	70·3	5·4	17·6
4-Acetyl	Yellow needles	95	,,	70·7	5·4	17·0	,,	,,	,,

* From ethyl acetate–ligroin. † From aqueous ethanol.
‡ Found: OMe, 13·4. Required: OMe, 13·7%. § Found: OMe, 13·2%.
‖ Found: Br, 29·3. Required: Br, 29·0%. ¶ Found: I, 39·4. Required: I, 39·3%.
** Found: I, 39·5%. †† Found: Cl, 15·5. Required: Cl, 15·3%.

4-Amino-2-methoxyazobenzene crystallized in orange plates, m. p. 157° (Found: C, 68·2; H, 5·8; N, 18·3. $C_{13}H_{13}ON_3$ requires C, 68·7; H, 5·7; N, 18·5%). *3-o-Chlorophenyl-1-phenyl triazen-3-carboxyanilide* formed white needles (from ether–ligroin), m. p. 111° (decomp.) (Found: C, 65·1; H, 4·3; N, 16·0. $C_{19}H_{15}ON_4Cl$ requires C, 65·1; H, 4·3; N, 16·0%), and *p-nitrophenylazomorpholine* yellow, bunched needles from ethanol, m. p. 81—82° (Found: C, 51·5; H, 5·2; N, 23·1. $C_{10}H_{12}O_3N_4$ requires C, 50·9; H, 5·1; N, 23·7%).

Results and Discussion

As noted on p. 701, owing to the instability of the reagents, the following conclusions are necessarily tentative.

The interpretation of the results obtained with halogen-substituted anilines is peculiarly difficult owing to the complex interplay of the *I* and *T* effects (see Table 2).

Table 1 summarizes the results obtained from amines not containing halogen atoms. To facilitate analysis of the products, non-reactive and reactive amines were allowed to compete with *m*- and *p*-bromoaniline, respectively, since these two compounds had been shown to give the most reproducible values. It can be seen that in this series there is a good correlation between the $\mu_{al.} - \mu_{ar.}$ values and the reactivity of the amine. In some

Table 1.

Substituent	$\mu_{al.} - \mu_{ar.}$	Reactivity: *p*	Reactivity: *m*	Electronic displacements	Remarks
CH_3	+0·45	28·4 ± 3·5	—	+*I*	Hyperconjugation is probably responsible for the high values obtained for this compound: *m*-toluidine gives much aminoazo-compound
OCH_3	*ca.* +0·05	2·8 ± 0·18	—	−*I*, +*T*	*T* > *I*, $\mu_{al.} - \mu_{ar.}$ by extrapolation from Sugden's values; *m*-anisidine gives aminoazo-compound
H	±0·00	1·0	1·0	—	Reference standard
$CO{\cdot}CH_3$	−0·18	0·04 ± 0·006	0·033 ± 0·002	−*I*, −*T*	
CN	−0·43	0·0013 ± 0·0002	0·0026 ± 0·0005	−*I*, −*T*	
NO_2	−0·88	0·00	0·00	−*I*, −*T*	Does not react
C_6H_5	—	>100	—	± *T*	Highly polarisable

cases, notably with *m*-anisidine and *m*-toluidine (Mehner, *J. pr. Chem.*, 1902, **65**, 401), the formation of large amounts of aminoazo-compound made the results valueless for purposes of comparison.

A similar relation can be observed in the reactivities of the monohalogenoanilines, the results for which are summarised in Table 2. The electronic displacements are in all

Table 2.

Substituent	Reactivity: *o*	Reactivity: *m*	Reactivity: *p*	$\mu_{al.} - \mu_{ar.}$
H	1·00	1·00	1·00	—
F	—	0·054 ± 0·003	0·018 ± 0·002	—
Cl	0·13 * ± 0·015	0·37 ± 0·07	0·68 ± 0·08	0·59
Br	0·18 † ± 0·04	0·027 ± 0·0005	3·37 ± 0·04	0·69
I	0·45 ± 0·1	1·1 ± 0·2	17·7 ± 2·5	0·86

* Naphthalene-β-diazonium sulphate used. † Corrected for solubility.

cases +*T*, −*I*, where *I* > *T*. The values are seen to tend in the same direction as the $\mu_{al.} - \mu_{ar.}$ values. The aberrant value found for *m*-bromoaniline cannot be explained, for it is highly reproducible (±2% in eight determinations) and cannot be due to experimental error.

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University of Sydney. [*Received, May 27th*, 1952].

142. *The Thermal Decomposition of Potassium Perchlorate.*

By L. L. Bircumshaw and T. R. Phillips.

The thermal decomposition of potassium perchlorate *in vacuo* and under small pressures of nitrogen has been investigated between 530° and 550°. Three methods were used, all of which gave results of poor reproducibility. *In vacuo*, chlorine as well as oxygen is produced by the decomposition, but it is absent when an inert gas is present. Potassium chlorate is produced during the decomposition and melting takes place. The results are not in complete agreement with recently published observations by Glasner and Simchen and it is suggested that this may be due to their use of impure crystals.

The decomposition of potassium perchlorate has been the subject of many researches. Teed (*J.*, 1887, **51**, 283) found that chlorate as well as chloride was formed, and stated that a solution of potassium perchlorate in potassium chlorate and chloride is decomposed at the boiling point of sulphur. Otto and Fry (*J. Amer. Chem. Soc.*, 1923, **45**, 1134) found neither chlorate nor chlorine in their reaction products. Crespi and Caamano (*Anal. Soc. Fís. Quím.*, 1936, **34**, 320, 901) found the addition of chloride to accelerate the reaction, which they suggested was autocatalytic. Hoffmann and Marin (*Sitzungsber. Preuss. Akad. Wiss. Berlin*, 1932, **27**, 3) carried out an extensive study of both the formation (from chlorate) and the decomposition of potassium perchlorate and studied the effect of additions of other substances. Most of the early work was done at atmospheric pressure in air. Sodeau (*J.*, 1900, **77**, 937) appears to have been the first to notice that small amounts of chlorine are produced in the decomposition of the chlorate. Since the commencement of the present work, Glasner and Simchen (*Bull. Soc. chim.*, 1950, **18**, 233) have reported data for a study of the decomposition of potassium perchlorate, *in vacuo*, at 480—540°. In all cases the rate–time curves showed two maxima, and by making interrupted runs, it was found that the maximum amount of chlorate corresponded to the minima in the rate curves.

Experimental

Materials.—From Hopkin and Williams's pure potassium perchlorate, three samples were prepared: "A" was recrystallised four times from water, "B" and "C" five times. A sample "An" was prepared from "AnalaR" potassium carbonate and "AnalaR" 72·7% perchloric acid. The solution of potassium carbonate was made just acid, boiled, and filtered hot, and the crystals obtained on evaporation and cooling were recrystallised four times. The samples all gave negative tests for chloride and chlorate ion. They also appeared to be free (spectroscopically) from traces of sodium.

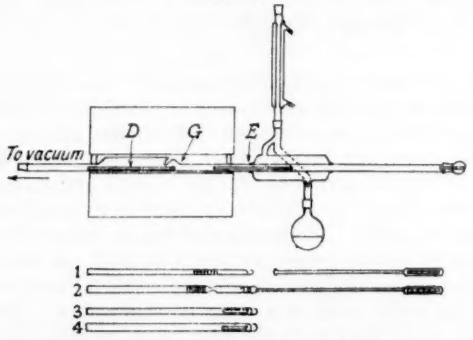
Experiments were made with: (i) Sample A, ordinary crystals, sieved and graded crystals, and crushed crystals; (ii) sample B, crushed crystals; samples C and An, crushed, graded crystals. Crystals were graded with B.S.S. sieves and were all stored in a vacuum-desiccator over P_2O_5. Crushing can best be described as squeezing the crystals in a mortar with a pestle, circular motion being avoided.

Apparatus.—The apparatus was almost identical with that used by Bircumshaw and Edwards (*J.*, 1950, 1800) with the following addition. To ensure that the material was perfectly dry, a drying unit was incorporated in the vacuum line (Fig. 1). It was arranged that the reaction tube *E* lay in the line surrounded by the outer jacket before being pushed into the reaction vessel at position *D*. It was heated in position *E* for 1 hour and then pushed into the furnace. Water was the usual heating liquid. The reaction tube was approx. 7" long and was introduced into the furnace by a magnetic "pusher" (Fig. 1, No. 1). If it were required to remove the tube from the furnace during the reaction, type 2 was used. Other types of reaction tube are shown in 3 and 4. A long tube was necessary, for otherwise, traces of potassium chloride would sublime out of it. In types 1 and 2 a glass-wool plug was used to "contain" the perchlorate in the tube. After a run it was usually found to contain some embedded potassium chloride. In some experiments the reaction tube and vapour jacket were tilted at 15° to the horizontal in the hope that the melted decomposition products would remain at one end of the tilted tube. A chromel–alumel thermocouple was introduced into the socket *G*. The method of measuring rates can best be illustrated by recording a sequence of measurements,

time (t) being in seconds : $t = 0$, pressure (I) in line measured with pumps in operation ; $t = 30$, pumps shut off from line ; $t = 60$, pressure (II) in line measured and pump switched on ; $t = 120$, pressure (III) in line recorded. The rate pressure was taken as (II) $- \frac{1}{2}$[(I) + (III)]. For " accumulatory " runs, the line was first evacuated, the pumps were shut off, and the increase in pressure on heating the salt was measured at regular intervals. The total volume of the apparatus was about 2850 c.c.

Results.—0·035 g. was found to be a suitable quantity of the perchlorate. Runs on the uncrushed and ungraded crystals showed considerable divergences. The crystals were then graded into two groups : A_1, bigger than 100 mesh ; A_2, 100—150 mesh. Differences were still

FIG. 1.



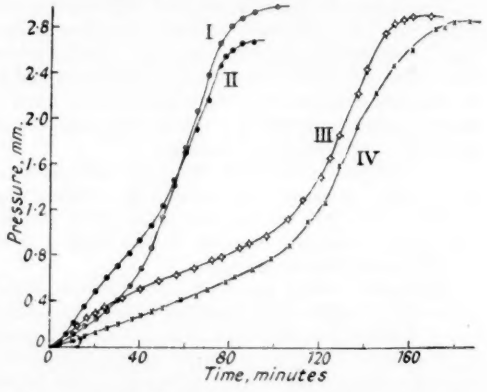
apparent. Decomposition took approx. 100 min. at 553° (Fig. 2). The appearance of the residue indicated that melting had taken place. The presence of chlorate (m. p. 370°) was confirmed in an interrupted run. The melting may therefore be connected with the formation to some extent of a ternary eutectic of these three salts.

It was thought that the differences observed might have been caused by the presence of small amounts of occluded solvent. A new sample of salt was therefore crushed as previously described, and dried in a desiccator ; runs were carried out at 541° but showed no greater agree-

FIG. 2.

I, II, *Sample A, crystals of mesh* 100—150. *Temp.*, 553°.

III, IV, *Sample B, crushed, ungraded. Temp.*, 541°.



ment (Fig. 2). The effect of drying the crystals in an evacuated vessel at 65° (P_2O_5) was investigated and also drying by prolonged pumping in the line, but little improvement was observed.

Sample C was prepared and sieved into five portions of mesh sizes : $C_a \pm 100$, C_b 100—150, C_c 150—200, C_d 200—300, $C_e < 300$. The preliminary drier was incorporated into the line and by means of the hook attachment (Fig. 1, No. 2) the contents of the tube were examined at various stages of the decomposition. It was found that during the first part of the reaction the solid gradually melted, the crystals first becoming " sticky " in appearance and finally coalescing. When this occurred gas evolution became much more rapid. The tube then contained a bubbling liquid which still had some lumps until the time when the maximum rate was reached whereupon the liquid became homogeneous. The liquid was splashed a considerable way along the tube

by the bubbles of gas. Trials of several types of tube to prevent this occurring were unsuccessful. The sublimate was separated from the main bulk of the residue by a clear zone, on which there was no deposit.

Finally, the sample An (from perchloric acid) was sieved to 30—32 mesh and those crystals used at 536° but with no better agreement. The reaction vessel was then tilted at 15° to the horizontal to avoid the spreading of the molten liquid but without effect.

Some " rate " runs were made on 0·080 g. of salt at 540°. The maximum rate occurred at a different time for every sample. The total time for reaction was of the same order as that for an accumulatory run (Fig. 3).

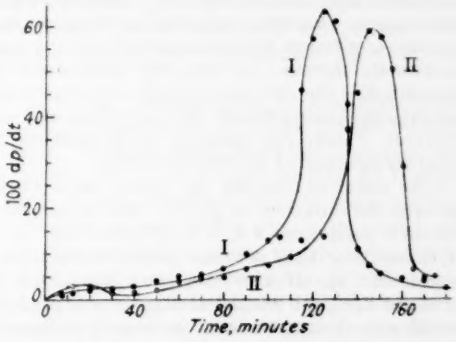


FIG. 3.
Sample An, mesh 30—52. Temp., 541°.
I, II, *Pure material.*

Two runs were made on crystals which had been obtained from a solution containing a considerable amount of potassium chloride. In curves for these two maxima were observed, the second being 2—3 times the height of the first (Fig. 4). Analysis of the salt showed that it contained 1·6% of chloride. Addition of solid chloride to perchlorate (0·005 g. to 0·075 g.) resulted in a much more rapid reaction, again with two maxima (Fig. 4).

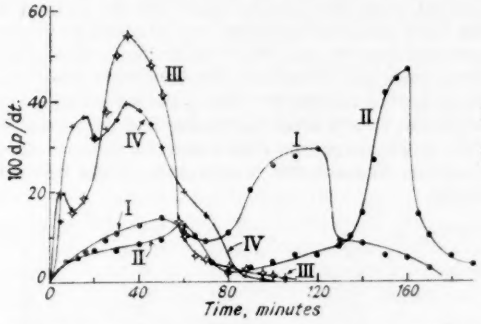


FIG. 4.
I *and* II, *Sample recrystallized from potassium chloride solution. Temp.*, 541°.
II *and* IV, *Sample mixed with solid potassium chloride. Temp.*, 541°.

The amount of chlorine given off was estimated by addition of potassium iodide solution and titration with standard N/100-arsenite from a micro-burette :

Wt. of $KClO_4$, g.	Loss, g.	Decompn., %	Cl, g.	Cl, %	pH of water	pH of solution
0·2000	0·0828	89·7	0·00045	0·87	5·98	6·83
0·1993	0·0854	92·7	0·00049	0·96	5·02	6·06

Chlorine is expressed as a percentage of the total weight of chlorine in the original sample. The residue was dissolved in distilled water and the solution made up to 50 c.c. in the first case and 25 c.c. in the second. The solution was then tested for alkalinity, and the pH values are as given above.

An attempt was made to estimate the chloride : chlorate ratio at the maximum decomposition rate. This could not be done very accurately as it was impossible to predict exactly when the maximum rate would occur. The experiments were made by taking rate measurements of the

Orig. $KClO_4$, g.	Time and temp. of decompn.	KCl, g.	$KClO_3$, g.	Loss in wt., g.	KCl/$KClO_3$ (w/w)
(1) 0·0814	134 min. at 540°	0·031	0·013	0·028	2·37
(2) 0·0800	146 ,, 540	0·022	0·014	0·022	1·59

decomposing material, and when the rate was approximately that of the maximum of previous runs the tube was removed and the contents analysed. The chloride ion was determined gravimetrically, and chlorate ion reduced with sulphur dioxide. The perchlorate ion is, of course, not reduced by sulphur dioxide.

Investigation of the Thermal Decomposition of $KClO_4$ *by Use of a Quartz Spiral Spring Balance.*—The construction of the balance will be described in another paper. The initial experiments were carried out on 50-mg. portions of the salt. The first experiment showed that when the evolved gases were continuously removed by pumping, and the pressure in the apparatus thus kept very low, the amount of residue lost on to the sides of the reaction vessel and on to the suspension fibre was considerable. The readings taken of the extension of the spring were thus meaningless. Further experiments were performed on 100-mg. portions, an initial small pressure of nitrogen being introduced into the apparatus and the evolved gases being allowed to accumulate therein. In this way sublimation was considerably reduced but not completely eliminated. The curves of weight loss–time were of a similar type at 530°, but, as with the experiments using pressure measurements, the variation from one sample to the next was considerable. There was, however, a fair agreement during the first part of every run, before the rapid acceleration of the rate took place.

The effect of varying the initial pressure of nitrogen was investigated. The variations between the runs were no greater than those observed with a constant nitrogen pressure. The pressures used were 1·4, 2·7, 10·8, and 10 cm. The most striking difference between these experiments and the previous pressure-measuring ones was that, with the exception of the first experiment, no chlorine was given off during the decomposition. This would explain why Otto and Fry (who worked at atmospheric pressure) did not observe the gas in their work on the perchlorate decomposition; its non-observance by Glasner and Simchen is not understood. The appearance of chlorine is prevented by an inert gas, which would suggest that the sublimation process and the production of chlorine are somehow related. Alternatively, they may be separate processes on which the nitrogen has the same effect, *viz.*, the prevention of the diffusion of the chlorine or potassium chloride vapour from the reaction mixture.

The composition of the contents of the bucket when melting was just about to take place was determined by analysis. As with the analysis of the mixture at the point of maximum rate, the exact moment for the removal of the bucket from the furnace could not be accurately foretold. The bucket was weighed before and after the decomposition, and the loss in weight found. In one case, the weight loss was determined directly from the contraction in the spring, but this method was not favoured, for if there were an immediate loss in weight when the bucket was lowered into the furnace this would not be recorded. This occurred because the bucket and spring took about two minutes to become steady after the bucket had been lowered into the furnace. The " zero " reading of the cathetometer was thus taken 2·5 minutes after lowering the bucket. This also allowed the sample to reach the temperature of the furnace. The results (see table) show reasonable agreement :

Sample	Wt. loss = wt. of O_2, g.	Wt. of residue, g.		Wt., g.	Wt., %	Mol., %
C			KCl	0·0061	6·43	11·0
(0·1005 g.)	0·0056	0·0949	$KClO_3$	0·0031	3·27	3·5
			$KClO_4$	0·0857	90·3	85·5
V			KCl	0·0061	6·5	11·3
(0·1000 g.)	0·0062	0·0938	$KClO_3$	0·0073	7·8	8·2
			$KClO_4$	0·0804	85·7	80·5
T			KCl	0·0067	7·2	12·5
(0·1000 g.)	0·0067	0·0935	$KClO_3$	0·0054	5·8	6·0
			$KClO_4$	0·0814	87·0	81·5

The three runs were carried out at 530°. Nitrogen pressure in the reaction vessel was 5·2 cm. for V and T, and 2·6 cm. for C.

The residue was dissolved in water and the chloride estimated gravimetrically as silver salt. When the chloride was known, the chlorate content could be calculated from a knowledge of the weight of oxygen liberated.

Some of the runs indicated that the rate of loss of weight was constant for the initial part of the reaction but, as usual with this reaction, it was difficult to reproduce this effect.

Discussion

The main difficulty observed during this reaction has been the variation of experimental results. In solid reactions, this is usually ascribed to differences in the nature of the surface

of the crystals, or to various defects present in the interior of the crystals. In this reaction, however, these causes have little effect, as after a certain time the whole system becomes molten. It is, therefore, useless to try and apply theories and equations, which have been derived for chemical reactions involving solid decompositions, to explain the results of this decomposition.

Some measure of agreement for different runs was sometimes observed in the initial stages of the reaction, and it is suggested that a true solid decomposition is then taking place. When the reaction rate accelerates, this is due to melting of the reactants. The melt produced evolves oxygen quite rapidly, until towards the end of the reaction, when the amount of potassium chloride produced causes the mixture to solidify once more. The melting is associated with the formation of a eutectic mixture of chloride, chlorate, and perchlorate.

The process of the reaction is therefore : (*a*) Initial decomposition of solid perchlorate with formation of chlorate and chloride. The chloride produced will accelerate the reaction and melting takes place. This does not occur all at once, and it has been observed that some parts of the mixture are molten before other parts. The melting can be brought about in two ways : (i) Local inhomogeneities in the mixture may result in some portions having the composition of an approximately eutectic mixture of the three salts, which will melt at the reaction temperature. These areas will eventually coalesce to give a completely molten mixture. (ii) When the rate of production of chlorate from the perchlorate is greater than its rate of decomposition, it will accumulate in the mixture, and because of its low melting point, molten chlorate will be formed. The other salts will dissolve in this to form a molten mixture of the three salts.

(*b*) This stage is the decomposition of the melt, which has the appearance of a boiling viscous liquid owing to evolution of bubbles of oxygen. This bubbling causes spreading of the reaction mixture along the reaction tube. The composition of the melt will not therefore be constant, and we may thus expect variations in the rate of gas evolution with every sample, depending on how much ' splashing ' has taken place.

(*c*) Finally, the melt solidifies owing to the chloride ultimately formed, and the rate of gas evolution becomes slower.

The reaction cannot be represented by any one stoicheiometric equation, and probably the decomposition is the net result of several simultaneous reactions, the following being some of the possibilities : $2KClO_4 \longrightarrow 2KCl + 4O_2$, $2KClO_4 \longrightarrow 2KClO_3 + O_2$, $4KClO_3 \longrightarrow 3KClO_4 + KCl$, $2KClO_3 \longrightarrow KClO_4 + KCl + O_2$.

The small quantity of chlorine evolved probably arises from the chlorate produced. This was observed by Sodeau (*loc. cit.*). There has been much conjecture whether it is actually produced by the decomposing potassium chlorate, or by the action of one of the products of the reaction on some other product, or on the original material. We have been unable to obtain any definite evidence on this point. In this connection it is noteworthy that the residue was slightly alkaline, which may be associated with the presence of small amounts of potassium oxide.

The occurrence of the two peaks in the rate runs obtained by Glasner and Simchen (*loc. cit.*) may be explained by the catalytic influence of the potassium chloride contained in their material (up to 0·40%). The presence of a small amount of potassium chloride alters the whole course of the reaction. No double peaks were found in the rate curves with the pure material used in the present work, but they were found when the material was contaminated with chloride.

Since the above paper was written, two papers have appeared on similar topics. Glasner and Weidenfeld (*J. Amer. Chem. Soc.*, 1952, **74**, 2464, 2467) used purer material than previously (Glasner and Simchen, *loc. cit.*) and obtained results more in agreement with the foregoing. Their work was done at atmospheric pressure and gave only poor reproducibility.

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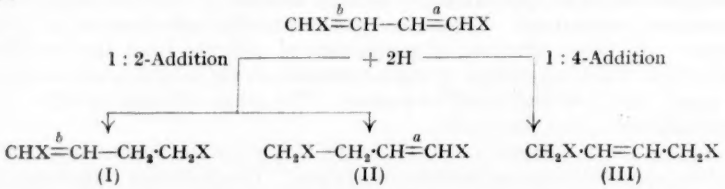
143. *Polyene Acids. Part V.* Catalytic Semi-hydrogenation of the Three Isomeric Muconic Acids and Confirmation of their Configurations.*

By J. A. Elvidge, R. P. Linstead, and John F. Smith

The geometrical configurations previously given to the three isomeric muconic acids have been confirmed by semi-hydrogenation. Under the same conditions the *cic-cis*-acid yields *cis*-Δ^{α}-dihydromuconic acid; the *trans-trans*-, the *trans*-Δ^{α}-dihydro-acid; and the *cis-trans*-acid a mixture of *cis*- and *trans*-Δ^{α}-dihydromuconic acids. *trans*-Δ^{β}-Dihydromuconic acid is a by-product in all these experiments. These results are discussed in the light of previous work.

In Part I of this series (*J.*, 1950, 2235), the preparation of the three geometrical forms of muconic acid was described and configurations were assigned to them. We now report the confirmation of these configurations by means of catalytic semi-hydrogenation.

The semi-hydrogenation of a conjugated diene of this type can be represented as follows:



If no inversion in configuration occurs, then the Δ^{α}-acid formed by 1 : 2-addition of hydrogen (I and II) can have either of the configurations *a* or *b* present in the original diene and if $a = b$ then only one Δ^{α}-acid will be formed. The three forms of muconic acid would thus give the following Δ^{α}-products: *cis-cis* → *cis*; *trans-trans* → *trans*; *cis-trans* → *cis* + *trans*. If, however, this line of attack were invalidated by inversion over the catalyst the same product would be expected from all three isomerides. Δ^{β}-Acid (III), formed by 1 : 4-addition, is a further possibility, but this is not immediately relevant to the argument and we return to this aspect later.

Literature on the catalytic semi-hydrogenation of conjugated dienes is scanty and, for the muconic acid system, contradictory. Thus Farmer and Hughes (*J.*, 1934, 304, 1929; cf. Farmer and Galley, *J.*, 1932, 430) isolated dihydro-acids but Ingold and Shah (*J.*, 1933, 885) obtained only complete hydrogenation. A likely explanation for this discrepancy arises from our work.

We have studied the hydrogenation of the neutral sodium salts of the three muconic acids over palladised charcoal with the results summarised in the Table. The products

Semi-hydrogenation of the muconic acids.

Starting material	Acids produced (%): Unchanged muconic	*cis*-Δ^{α}-Dihydro-muconic	*trans*-Δ^{α}-Dihydro-muconic	Δ^{β}-Dihydro-muconic	Adipic
(a) *trans-trans*	0	0	76	13	12
(b) *cis-trans*	21	22	50	11	0
(c) *cis-cis*	18	56	0	10	17
(d) 1 : 1 Mixture of *cis-cis* and *trans-trans*	19 (13% *cis-cis*, 6% *trans-trans*)	33	34	11	12

were analysed by a method (described in the Experimental section) which is more accurate than that of Farmer and Hughes (the order of accuracy may be gauged by the divergence of the total yields from 100%). The first point which emerges is that good yields of dihydro-

* Part IV, *J.*, 1952, 1026.

acids were obtained under our experimental conditions, as in Farmer's work. The second is that the Δ^{α}-dihydro-acids from the symmetrical muconic acids were strictly homogeneous, whereas the Δ^{α}-product from the *cis-trans*-muconic acid was a mixture of the *cis*- and the *trans*-form. The configurations of the three muconic acids are therefore confirmed.

The *trans*-Δ^{α}-dihydromuconic acid (isolated as the half methyl ester) was identified by comparison with authentic material (Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228). The *cis*-Δ^{α}-acid agreed with Farmer and Hughes' description (*loc. cit.*) and its structure was confirmed by its inversion to the *trans*-isomeride by cold dilute hydrochloric acid containing a trace of sulphur dioxide. The same inversion could not be brought about by irradiation with ultra-violet light in the presence of iodine. Pure *cis-cis*-muconic acid is easily inverted by this means although its inversion does not occur in the presence of its semi-hydrogenation products.

The Table shows that the *cis*-double bond is hydrogenated rather more readily than the *trans* when they are in direct competition within the same molecule: a similar difference is not, however, shown by the experiments with an equimolecular mixture of symmetrical acids [Section (d) of Table].

Δ^{β}-Dihydromuconic acid was formed in all our experiments, presumably by direct 1 : 4-addition. The Δ^{β}-acid isolated from the semi-hydrogenation of *cis-cis*-muconic acid was the well-known and presumably *trans*-form, m. p. 195°, and appeared to be free from *cis*-isomeride. The formation of a *trans*-Δ^{β}-acid from *cis-cis*-muconic acid indicates that the diene system is adsorbed on the catalyst in an *s-trans*-form. This is the preferred configuration for the acid on general grounds (see Part I, *loc. cit.*). The stereochemical aspect of 1 : 4-hydrogenation is especially interesting and is being investigated further.

The fact that dihydro-acids were obtained in good yields in our experiments and those of Farmer and his collaborators means that in aqueous solution the muconate ions must be more readily hydrogenated than their dihydro-products. Rate measurements supported this. In methanol over palladised charcoal the rate of hydrogen uptake by *cis-cis*-muconic acid was some 6 times that of the ions in water. Equivalent amounts of *trans*-Δ^{α}- and -Δ^{β}-dihydromuconic acid were hydrogenated about as rapidly under these conditions, but *cis*-Δ^{α}-dihydromuconic acid at only half the rate. Yet semi-hydrogenation of *cis-cis*-muconic acid in alcohol gave less than 5% of *cis*-Δ^{α}-dihydromuconic acid, the reaction mixture consisting largely of adipic acid and starting material. Measurements on separated components or systems are therefore not necessarily pertinent. Ingold and Shah's result (see above) with (*trans-trans*-)muconic ester may well be attributable to their use of alcohol as medium.

Experimental

Partial Hydrogenation of the Muconic Acids.—(*a*) *trans-trans*- (10 g.) and (*b*) *cis-trans*-Muconic acid (10 g.), in water (*a*, 150 c.c.; *b*, 200 c.c.) containing sodium hydrogen carbonate (12 g.), were separately shaken with 5% palladium–charcoal (0·5 g.) in hydrogen (allowed uptake: *a*, 1760 c.c. at 771 mm./15°, in 65 minutes; *b*, 1705 c.c. at 743 mm./16°). (*c*) Sodium *cis-cis*-muconate (from 10 g. of acid), and (*d*) a mixture of the *cis-cis*- (5 g.) and *trans-trans*-acid (5 g.), in water (*c*, 200 c.c.; *d*, 200 c.c. containing 12 g. of sodium hydrogen carbonate), were similarly semi-hydrogenated.

Separation of the Products.—This will be exemplified by the product from experiment (*d*). The filtered solution was acidified with hydrochloric acid, and the precipitate washed with water. Washings and filtrate were combined. Extraction of the precipitate with hot ethanol gave (*A*) insoluble *trans-trans*- and (*B*) soluble *cis-cis*-muconic acid. The preceding aqueous filtrate was extracted exhaustively with ether, the extract evaporated, and the residue extracted with boiling benzene. The soluble portion (*C*), *cis*-Δ^{α}-dihydromuconic acid, was recrystallised from benzene and had m. p. 78—80°, and the insoluble (*D*) was partially esterified (3 days at room temperature) in ether (*ca.* 10 vols.) with methanol (2—3 fold excess) containing 0·1% of hydrogen chloride. These mild conditions esterify adipic and Δ^{β}-dihydromuconic acid completely: the amount of *trans*-Δ^{α}-dihydro-acid converted into diester is appreciable but much smaller than by the method of Farmer and Hughes (*loc. cit.*). The neutral-ester fraction was hydrolysed by brief boiling with 2N-sodium hydroxide (slight excess) to yield a mixture (*E*) of Δ^{β}-dihydromuconic and adipic acid, with some *trans*-Δ^{α}-dihydromuconic acid. Extraction of

the acidic fraction (from the esterification) with light petroleum removed (*F*) (δ)-methyl hydrogen *trans*-Δ^{α}-dihydromuconate,* m. p. 58°. Insoluble residue (*G*) was *cis-cis*-muconic acid.

The product from experiment (*a*) on similar treatment yielded nothing at points (*B*), (*C*), and (*G*) in the above scheme. Experiment (*b*) gave *cis-trans*-muconic acid at (*G*), but no product at (*A*) and (*B*). Experiment (*c*) afforded a mixture of *cis-cis*-muconic and adipic acid at (*B*) and *cis-cis*-muconic acid at (*G*), but no product at (*A*) and (*F*) and no *trans*-Δ^{α}-dihydro-acid in the mixture at (*E*).

Analysis of the Separated Products.—Unchanged *trans-trans-*, *cis-cis-*, or *cis-trans*-muconic acid, and *cis*-Δ^{α}-dihydromuconic acid were weighed at (*A*), (*B* + *G*), (*G*), and (*C*), severally. When *cis-cis*-muconic acid at (*B*) was contaminated with adipic acid, hydrogenation and/or bromometric analysis (see below) gave the relative proportions. The removal of *cis*-Δ^{α}-dihydro-acid at (*C*) prevented interference with bromometric analyses at later stages. At (*D*), portions of the benzene-insoluble material were hydrogenated quantitatively and analysed bromometrically to give, respectively, total unsaturation (i) and Δ^{β}-dihydromuconic acid (ii). At (*E*), hydrogenation gave total dihydro-acids there present (iii), and bromometric analysis the Δ^{β}-dihydromuconic acid (iv). Agreement between the values (ii) and (iv) showed that there was no loss of Δ^{β}-dihydro-acid to (*F*) and (*G*). Adipic acid at (*E*) was given by 100 − (iii)%, and *trans*-Δ^{α}-dihydromuconic acid by (iii) − (iv), the remainder being isolated at stage (*F*) as the half methyl ester. A check on the hydrogenation values was available because (i) − (iii) represented the muconic plus *trans*-Δ^{α}-dihydromuconic acids, later isolated at (*G*) and (*F*).

The experimental values are recorded in the Table.

Bromometric Analysis for Δ^{β}-Dihydromuconic Acid in the Mixtures (D) and (E).—Calibration studies. The *trans*-Δ^{β}- and -Δ^{α}-dihydromuconic acids and iodine in ethanol, or their sodium salts in water and iodine in potassium iodide, did not react appreciably during several hours. Bromine in chloroform reacted at a convenient rate. Solutions of *trans*-Δ^{β}- (758 mg.), *trans*-Δ^{α}-dihydromuconic (109 mg.), and *cis-cis*-muconic acid (723 mg.) in ethanol (5 c.c. portions) were separately treated with 2% bromine in chloroform (50 c.c.), and the solutions diluted with chloroform to 250 c.c. in dark flasks. 25-C.c. aliquots were withdrawn at intervals and the unchanged bromine was determined iodometrically (% uptake of 2 atoms of Br, severally : 70, 21, 14 in 5 minutes; 82, 28, 18 in 10 minutes; 92, 38, 22 in 20 minutes; 100, 49, 28 in 40 minutes; 102·5, 64, 36% in 80 minutes). The greater rate of reaction of the Δ^{β}-dihydro-acid enabled it to be determined in mixtures.

Binary mixtures (70—75 mg.) of *trans*-Δ^{β}-dihydromuconic acid with *cis-cis*-muconic and *trans*-Δ^{α}-dihydromuconic acid were separately dissolved in methanol (5-c.c. portions) in dark flasks. To each solution, chloroform (10 c.c.) was added and then freshly standardised 1% bromine in chloroform (10·0 c.c.). After 10 minutes, the unchanged bromine was determined iodometrically. The % uptake of 2 equivs. of Br in 10 minutes (% reaction) was plotted against % of Δ^{β}-dihydro-acid in the mixtures. The two curves for the two series of mixtures were almost coincident. Thus *cic-cis*-muconic acid behaved effectively as Δ^{α}-dihydro-acid and could be reckoned as such (with equiv. 72) in the calculation of the bromometric analyses, with negligible error. The mean of the two curves was used, given by :

Δ^{β}-Acid, %	0	10	20	30	40	50	60	70	80	90	100
Reaction, % (defined)	15	22·5	29·5	36·5	43	49·5	55·5	60·5	64	66·5	68

Adipic acid (72 mg.) reacted under the standard conditions to the extent of 7%.

Method. The samples taken at (*D*) and (*E*) of weights chosen to contain 70—75 mg. of unsaturated acids (" effective dihydro-acids "), respectively calculated from the values (i) and (*G*), and (iii), were treated with 1% bromine in chloroform under the foregoing standard conditions. The apparent % reaction was corrected for the adipic acid present (x%) {at (*D*), [100 − (iii)](*E*)/(*D*); at (*E*), 100 − (iii)%} by deducting 7% of x. The % of Δ^{β}-acid in the unsaturated acids was then read from the curve described. Finally, the % of Δ^{β}-acid in the sample was calculated.

The accuracy of the analyses exemplified below showed that the method used for binary mixtures could be extended to ternary and quaternary mixtures; and also justified the other approximations.

Examples. (*a*) 119·0 Mg. of an artificially prepared mixture of *trans*-Δ^{β}- and *trans*-Δ^{α}-dihydromuconic acid, containing 39·0% of adipic acid (∴ 61% of dihydro-acids, equiv., 72), consumed under the standard conditions bromine equivalent to 11·20 c.c. of 0·0508N-thiosulphate.

* For nomenclature see *J.*, 1951, 3386.

Apparent amount of reaction = 11·2 × 0·0508 × 100 × 72 × 100/(61 × 119) = 56·4%.
Correction for adipic acid = 39 × 7/100 = 2·7.

Hence, amount of reaction = 53·7%, whence (from graph) amount of Δ^{β}-dihydro-acid in the mixed dihydro-acids = 57%. Therefore amount of Δ^{β}-dihydro-acid in the ternary mixture = 61 × 57/100 = 34·7% (Given : 34·9%).

(*b*) 158·6 Mg. of a mixture of *trans*-Δ^{β}-, *trans*-Δ^{α}-dihydromuconic, and *cis-cis*-muconic acid containing 48·2% of adipic acid (∴ 51·8% of "effective dihydro-acids," equiv., *ca.* 72), consumed under the standard conditions bromine equivalent to 10·20 c.c. of 0·0508 N-solution.

Apparent amount of reaction = 10·2 × 0·0508 × 100 × 72 × 100/(51·8 × 158·6) = 45·4%.

Reaction, corrected for adipic acid = 42·0%, whence (from graph) Δ^{β}-dihydro-acid in the mixed unsaturated acids = 38·2%. Therefore, Δ^{β}-dihydro-acid in the quaternary mixture = 51·8 × 38·2/100 = 19·8% (Given : 20·1%). (The amount of *cis-cis*-muconic acid in the mixture was 10%.)

Isolation of trans-Δ^{β}-*Dihydromuconic Acid.*—Sodium *cis-cis*-muconate (10 g.) in water (200 c.c.) and 5% palladium–charcoal (0·2 g.) were shaken in hydrogen until 1 l. had been taken up (Calc. for 1 double bond : 1·7 l.). The filtered solution was acidified with hydrochloric acid and the precipitated *cis-cis*-muconic acid (3·9 g.) washed with cold water. The filtrate and washings were extracted continuously with ether overnight, and the solid residue from the extract was crystallised from benzene, yielding *cis*-Δ^{α}-dihydromuconic acid (4·6 g.). The benzene-insoluble portion (0·6 g.) was esterified partially (under the conditions given above) and the neutral fraction hydrolysed with cold 2N-sodium hydroxide. Acidification precipitated an acid (0·17 g.), m. p. 194—195° alone and when mixed with authentic *trans*-Δ^{β}-dihydromuconic acid (Farmer and Hughes, *loc. cit.*).

Isomerisation of cis-Δ^{α}-*Dihydromuconic Acid.*—A solution of the acid (1·5 g.) in N-hydrochloric acid (20 c.c.), containing a trace of sulphur dioxide, deposited crystals (0·41 g.), m. p. 190—192°, when kept for 7 days. Continuous extraction of the filtrate with ether yielded a solid, which was extracted with boiling benzene. The benzene-insoluble solid (0·56 g.) was combined with the foregoing crystals. Recrystallisation from water gave *trans*-Δ^{α}-dihydromuconic acid (0·96 g.), m. p. and mixed m. p. 190—192°.

The *cis*-Δ^{α}-acid (0·3 g.) in ethanol containing a trace of iodine was recovered (m.p. 78—80°) after irradiation for 5 hours with ultra-violet light from a Hanovia lamp.

Hydrogenation Rate Measurements.—Methanol. The dihydro-acids (0·5 g. of each) and muconic acid (0·25 g.) in methanol (30-c.c. portions) were hydrogenated (at 16°/762·5 mm.) over 5% palladium–charcoal (0·1-g. portions) :

	Uptake (c.c.)			
Time (min.)	*cis*-Δ^{α}	*trans*-Δ^{α}	*trans*-Δ^{β}	*cis-cis*-
3	8	17	22	24
5	15	27	34	38
7	22	36	47	48
10	29	50	62	61
12	36	59	68	69
14	39	68	71	74
16	43	72	—	—
18	46	73	—	—
36	69	—	—	—

Aqueous alkali. The acids were similarly hydrogenated in 5% aqueous sodium carbonate (30-c.c. portions) :

	Uptake (c.c.)				Uptake (c.c.)		
Time (min.)	*trans*-Δ^{α}	*trans*-Δ^{β}	*cis-cis*-	Time (min.)	*trans*-Δ^{α}	*trans*-Δ^{β}	*cis-cis*-
5	5	9	10	40	42	41	63
10	11	16	20	50	51	48	72
15	16	21	30	70	67	61	85
20	21	26	39	100	85	79	91
30	32	34	53				

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144. *Xylopic Acid. Part I.*

By Hussein A. Fahim and Ibrahim R. Shimi.

Xylopic acid, $C_{22}H_{32}O_4$ (Fahmy, El Deeb, and Karawya, *Proc. Pharm. Soc., Egypt*, 1951, **33**, 33) has been obtained in improved yield from the pericarp of *Xylopia æthiopica*, by the use of low-boiling light petroleum or aqueous pyridine. The acid gave a methyl ester, acid chloride, and amide. It exhibted no reducing properties, did not contain alkoxyl groups, and did not react with *p*-nitrophenylhydrazine, acetic anhydride, or benzoyl chloride. The absence of selective absorption between 200 and 400 mμ suggests that chromophoric groups are absent.

Experimental.—Xylopic acid. The acid formed small plates, m. p. 265—266°, $[\alpha]_D^{29.5}$ −127° (in $CHCl_3$) [Found: C, 73·8, 74·0, 73·7; H, 8·9, 9·1, 9·3%; *M* (Rast), 368, 361; equiv. (by titration), 358·9, 357·4, 359·8, 360·3. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·9%; *M*, 360·5]. It was sparingly soluble in carbon disulphide, ether, and acetone, and sparingly soluble in light petroleum.

Derivatives. Treatment with diazomethane or methyl sulphate gave the *methyl* ester as plates, m. p. 124° (Found: C, 73·8; H, 9·1. $C_{23}H_{34}O_4$ requires C, 73·8; H, 9·1%). The acid chloride was prepared by refluxing the acid with excess of oxalyl chloride for 6 hours; treatment with ammonia then gave the *amide*, microscopic plates [from ethyl acetate–light petroleum (b. p. 40—60°)], m. p. 196—198° (decomp.) (Found: C, 73·4; H, 9·1; N, 3·4, 3·5, 3·6. $C_{22}H_{33}O_3N$ requires C, 73·5; H, 9·2; N, 3·9%).

Action of nitric acid. The acid was treated with a mixture of fuming and concentrated nitric acid (equal volumes) at 5—20° for 1 hour. The white product was purified by repeated treatment with benzene and light petroleum (b. p. 80—100°), giving a nitrogenous acid, m. p. 146° (decomp.) (Found: equiv., 301·3, 303·8).

The authors thank the Pharmacognosy Department for providing them with some xylopic acid extracts and the fruits, and Dr. M. H. Shaker, Biochemistry Dept., Fouad I Institute of Tropical Diseases, for providing the absorption spectrum data.

Fouad I University, Cairo, Egypt. [*Received, May 27th*, 1952.]

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145. *The Stereochemistry of Scopolamine.*

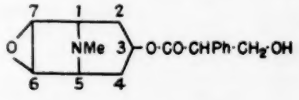
By Jerrold Meinwald.

Although no experiments designed to elucidate the stereochemistry of scopolamine (I) have been recorded, it is possible to assign unambiguously configurations to all five asymmetric centres in the bicyclic nucleus on the basis of facts already known (Henry, "The Plant Alkaloids," J. and A. Churchill, Ltd., London, 1949; Manske and Holmes, "The Alkaloids," Academic Press, New York, 1950, Vol. I).

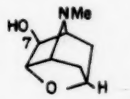
The key is the structure of a hydrolysis product, scopoline, which requires the configuration (II). The oxide bridge of scopoline must be *trans* to the nitrogen bridge if the structure is to be sterically possible. The hydroxyl group at $C_{(7)}$ would be expected to be *trans* to the oxide bridge, since it must be formed by an internal nucleophilic opening of a *cis*-epoxide (Bartlett, *J. Amer. Chem. Soc.*, 1935, **57**, 224; Wilson and Lucas, *ibid.*, 1936, **58**, 2396). Thus, scopine, the immediate precursor of scopoline, must be (III) in order to satisfy the geometrical requirements for the internal displacement reaction. It would be difficult to envisage a path for the exceedingly ready rearrangement of scopine to scopoline if the displacing $C_{(3)}$-hydroxyl group were not *trans* to both the nitrogen bridge and the epoxide ring. Finally, since normal ester hydrolysis does not alter the configuration of the alcoholic component (cf. Alexander, "Principles of Ionic Organic Reaction Mechanisms," J. Wiley and Sons, New York, 1950), scopolamine itself must be represented by (IV).

Confirmatory evidence is provided by the novel transformations which occur when scopolamine is treated with hydrogen peroxide. Two epimeric *N*-oxides would normally

be expected. In fact, one such oxide (V) is the chief product. A secondary product, however, can be isolated as a crystalline, tetracyclic, quaternary bromide (VII), the formation of which is best represented as an internal displacement of tropate anion from the epimeric *N*-oxide (VI). This change emphasizes the necessity of a *trans*-relation



(I)



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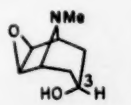

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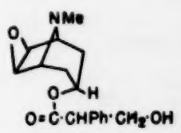
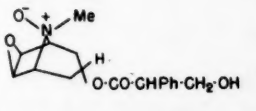
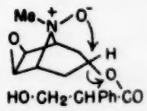


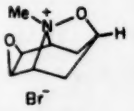
(IV)



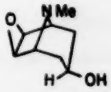
(V)



(VI)



(VII)



(VIII)

between the nitrogen bridge and the oxygen atom at $C_{(3)}$ in scopolamine itself. *pseudo*-Scopine, the product of chemical reduction of scopolinium bromide (VII), is then seen to have the $C_{(3)}$-hydroxyl group *cis* to the nitrogen bridge, as shown in (VIII). It is stable under the conditions which convert scopine into scopoline, as would be expected.

[Added, Oct. 1st, 1952.] Since the submission of this Note, a similar conclusion has been recorded independently by Fodor (*Nature*, 1952, **170**, 278).

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146. *Chloramines as a Source of Iodine Chloride. The Preparation of Iodo-phenols, -naphthols, and -aromatic Ethers by Means of a Chloramine and an Iodide.*

By BRYNMOR JONES and EILEEN N. RICHARDSON.

THE value of chloramines as chlorinating agents has long been established but, as Chattaway (*J.*, 1905, **87**, 145) and Orton (*Proc.*, 1909, **25**, 306) showed, the nature of the halogenating agent to which they give rise is determined by the nature of the halogen acid added, in accordance with the equation, $>NCl + HX = >NH + XCl$; *e.g.*, using dichloramine-T and hydrogen iodide, or, better, sodium iodide, Bradfield, Orton, and Roberts (*J.*, 1928, 782) readily prepared an acetic acid solution of iodine chloride suitable for use in the iodination of anilines. This reagent has now been applied to the iodination of phenols, hydroxybenzoic and hydroxynaphthoic acids, and aromatic ethers.

The range of such compounds which can conveniently be iodinated is limited by their susceptibility to oxidation and by the ease with which they undergo substitution. Highly reactive compounds, such as phenol, *p*-cresol, α- and β-naphthols, and even 4-chloro-1-naphthol undergo both iodination and oxidation, and give rather intractable tarry products. Less reactive hydroxy-compounds, such as the mono-halogeno- and -nitro-phenols, and the hydroxybenzoic acids, with one equivalent of the reagent, give mixtures of mono- and di-iodo-derivatives which are not easily separated: with two equivalents they give high yields of the di-iodo-compounds. On the other hand, 2 : 4-dihalogenophenols, 3-nitro-*p*-cresol and 3- and 6-hydroxy-2-naphthoic acids give excellent yields of the monoiodo-derivatives. Of the ethers examined, only those formed from the more reactive hydroxy-compounds undergo iodination smoothly. Others, such as *p*-bromoanisole, anisic acid, benzyl 4-chloro-1-naphthyl ether, and 4-ethoxy-1-naphthoic acid, do not react appreciably. The behaviour of the three isomeric dimethoxybenzenes shows that the *m*-isomer alone gives a high yield of a di-iodo-derivative. The yields of pure

products from the *m*-, *o*-, and *p*-isomers were 75, 30, and 20% respectively (cf. de la Mare and Vernon, *J.*, 1951, 1764).

The following table summarises the principal results obtained.

(M. p.s are uncorrected. Microanalyses were carried out by Drs. Weiler and Strauss, Oxford.)

Reactant	ICl, equiv.	Products	M. p.*	Yield, %	Formula	Found, % C	Found, % H	Reqd., % C	Reqd., % H
Anisole	1	*p*-Iodoanisole	52°	90	—	—	—	—	—
Phenetole	1	*p*-Iodophenetole	27	90	—	—	—	—	—
2-Naphthyl methyl ether	1	1-Iodo-2-naphthyl methyl ether	88	90	$C_{11}H_9OI$	47·0	3·3	46·5	3·2 [1]
2-Naphthyl ethyl ether	1	*Ethyl 1-iodo-2-naphthyl ether*	74	87	$C_{12}H_{11}OI$	48·3	4·1	48·3	3·7
1-Naphthyl ethyl ether	1	*Ethyl 4-iodo-1-naphthyl ether*	45	82	—	48·4	3·6	,,	,,
2 : 4-Dichlorophenol	1	2 : 4-Dichloro-6-iodophenol	62	80	—	—	—	—	— [2]
2 : 4-Dibromophenol	1	2 : 4-Dibromo-6-iodophenol	104	80	—	—	—	—	— [3]
3-Nitro-*p*-cresol	1	5-Iodo-3-nitro-*p*-cresol	83	90	$C_7H_6NO_3I$	30·2	2·0	30·1	2·2 [4]
2-Chloro-*m*-5-xylenol	1	2-Chloro-4-iodo-*m*-5-xylenol and 2-Chloro-4 : 6-di-iodo-*m*-5-xylenol	90 131	65	C_8H_8OClI	34·3	2·9	34·0	2·9 [5]
2-Chloro-*m*-5-xylenol	2	2-Chloro-4 : 6-di-iodo-*m*-xylenol	131	95	$C_8H_7OClI_2$	23·6	2·1	23·5	1·8
2 : 4-Dichloro-*m*-5-xylenol	1	2 : 4-*Dichloro*-6-*iodo*-m-5-*xylenol*	130	90	$C_8H_7OCl_2I$	30·2	2·2	30·3	2·2
Salicylic acid	2	3 : 5-Di-iodosalicylic acid	233	85	—	—	—	—	— [6]
p-Hydroxybenzoic acid	2	4-Hydroxy-3 : 5-di-iodobenzoic acid	262* (255°)	90	$C_7H_4O_3I_2$	22·0	1·2	21·5	1·0 [7]
3-Hydroxy-2-naphthoic acid	1	3-*Hydroxy*-4-*iodo*-2-*naphthoic acid*	d. (210°)	80	$C_{11}H_7O_3I$	42·1	2·3	42·0	2·2
6-Hydroxy-2-naphthoic acid	1	6-*Hydroxy*-5-*iodo*-2-*naphthoic acid*	234 (223°)	92	$C_{11}H_7O_3I$	42·1	2·1	42·0	2·2
6-Methoxy-2-naphthoic acid	1	5-*Iodo*-6-*methoxy*-2-*naphthoic acid*	d. (292°)	90	$C_{12}H_9O_3I$	44·0	2·7‡	43·9	2·7
6-*n*-Lauroyloxy-2-naphthoic acid	1	5-*Iodo*-6-n-*lauroyloxy*-2-*naphthoic acid*	†	90	$C_{23}H_{31}O_3I$	57·5	6·4	57·2	6·5 [8]
7-*n*-Octyloxy-2-naphthoic acid (m. p. 141°)	1	8-*Iodo*-7-n-*octyloxy*-2-*naphthoic acid*	148	90	$C_{19}H_{23}O_3I$	53·8	5·3	53·5	5·4
7-*n*-Cetyloxy-2-naphthoic acid (m. p. 137°)	1	7-n-*Cetyloxy*-8-*iodo*-2-*naphthoic acid*	123	90	$C_{27}H_{39}O_3I$	60·4	7·5	60·2	7·3
m-Dimethoxybenzene	2	4 : 6-*Di-iodo*-1 : 3-*dimethoxybenzene*	198—199	75	$C_8H_8O_2I_2$	24·9	2·0	24·7	2·1 [9]
o-Dimethoxybenzene	2	4 : 5-Di-iodo-1 : 2-dimethoxybenzene	134	30	—	24·9	2·3	,,	,, [10]
p-Dimethoxybenzene	2	2 : 5-Di-iodo-1 : 4-dimethoxybenzene	171	20	—	24·9	2·1	,,	,, [11]
Methyl *m*-5-xylyl ether	2	2 : 4-*Di-iodo*-3 : 5-*dimethylphenyl methyl ether*	125	50	$C_9H_{10}OI_2$	27·9	2·5	27·8	2·6

* Temperatures in parentheses are those at and above which iodine is evolved; d. = decomp.
† Mesomorphic: smectic phase 145—167°, nematic phase 167—170°.
‡ Found: I, 38·5. Calc. for $C_{12}H_9O_3I$: I, 38·7%.

[1] Ray and Moonaw (*J. Amer. Chem. Soc.*, 1933, **55**, 3833) record m. p. 88°. [2] Kohn and Sussman (*Monatsh.*, 1925, **46**, 594) give m. p. 63°. [3] Kohn and Sussman (*loc. cit.*) record m. p. 106°; Brenans and Girod (*Compt. rend.*, 1928, **186**, 1130) give m. p. 104°. [4] Datta and Prosad (*J. Amer. Chem. Soc.*, 1917, **39**, 446) give m. p. 83·5°. [5] Bordeianu (*Ann. Sci. Univ. Jassy*, 1937, **23**, 240; *Chem. Abs.*, 1938, 5802) gives m. p.s of 92—93° and 131—132°, respectively. [6] Woollett and Johnson (*Org. Synth.*, 1934, **14**, 52) give m. p. 235—236°. [7] Woollett and Johnson (*loc. cit.*) record m. p. 278—279° (corr.). [8] Cf. Gray and Brynmor Jones (*Nature*, 1951, **167**, 83; 1952, **170**, 451). [9] Cf. Meerwein, Hoffmann, and Schill (*J. prakt. Chem.*, 1940, **154**, 266). [10] G. M. Robinson (*J.*, 1916, **109**, 1086) gives m. p. 132°. [11] G. M. Robinson (*loc. cit.*) records m. p. 171°.

In the majority of cases the reagent was added cautiously to a well-stirred solution of the phenol or ether in acetic acid at room temperature, but, because of their low solubility, the

hydroxy- and alkoxy-naphthoic acids were iodinated at 60—75°. Occasionally some of the products were in part deposited from solution, but generally they were isolated by dilution to 50% acetic acid. At this dilution little toluenesulphonamide separated, and the iodo-derivatives were readily purified by crystallisation from alcohol or acetic acid.

Grateful acknowledgment is made to the Distillers Co. Ltd. and to Imperial Chemical Industries Limited for grants to the Department. The authors are also indebted to the Department of Scientific and Industrial Research for a maintenance grant to one of them, and to Mr. G. W. Gray, B.Sc., for samples of the alkoxynaphthoic acids.

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147. *The Volatile Oil of* Metrosideros scandens.

By A. J. BIRCH.

GARDNER (*J. Soc. Chem. Ind.*, 1931, **50**, 141T) found the oil of *Metrosideros scandens* to contain a high proportion of a sesquiterpene hydrocarbon which by dehydrogenation gave cadalene and an unidentified azulene, and by the action of hydrogen chloride gave what appeared to be (+)-cadinene dihydrochloride. Its physical constants were in agreement with a tricyclic structure, and the formation of azulene and naphthalene derivatives from the same substance would make the structure of considerable interest. We find the reactions of this sesquiterpene to be explained by its containing (−)-aromadendrene and (−)-cadinene or a cadinene isomer.

Experimental.—A specimen of the oil (50 c.c.) was kindly given to the author by Dr. W. I. Taylor who had collected and distilled it near Auckland (N.Z.). Distillation, followed by fractionation over sodium, gave fractions (i) (21 c.c.) b. p. 96°/2 mm., $[\alpha]_D$ −22°, n_D^{18} 1·5010, d_{18}^{18} 0·9202 (Found: C, 88·3; H, 11·9. Calc. for $C_{15}H_{24}$: C, 88·2; H, 11·8%), and (ii) (6 c.c.) b. p. 100—102°/2 mm., $[\alpha]_D$ −80°.

Fraction (i) was principally (−)-aromadendrene. It had infra-red bands at 6·06 and 11·27 μ due to $C(CH_3)_2$, and was converted by ozonolysis into formaldehyde (2 : 4-dinitrophenylhydrazone, m. p. 177°) and α-*apo*aromadendrone, m. p. 71°, $[\alpha]_D$ −5·6° in EtOH, which gave rise on the steam-bath to *apo*aromadendrone, $[\alpha]_D$ +3·5° in EtOH, m. p. 83—84° undepressed by an authentic specimen kindly supplied by Professor F. N. Lahey (Brisbane). Dehydrogenation with sulphur at 280° (3 minutes) followed by chromatography in light petroleum (b. p. 40—60°) on alumina gave guaiazulene, identified as its trinitrobenzene complex, m. p. 150—151°, undepressed by an authentic specimen (m. p. 151—152°) kindly supplied by Dr. A. Fürst (Zurich); no cadalene could be detected. The action of hydrogen chloride in ether on the hydrocarbon gave no crystalline product.

Fraction (ii) on dehydrogenation and chromatography as above gave cadalene, identified as the trinitrobenzene complex, m. p. and mixed m. p. 113°. No azulene was formed. Dry hydrogen chloride gave (+)-cadinene dihydrochloride, m. p. 117°. The structure of this derivative was confirmed by refluxing it with sodium acetate in acetic acid and dehydrogenating the product as above to cadalene (trinitrobenzene complex, m. p. 113°).

M. p.s are corrected.

This work was carried out during the tenure of the Smithson Fellowship of the Royal Society.

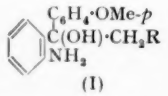
UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October* 20*th*, 1952.]

148. *The Use of Sodamide in Preparation of 2- and 3-Pyridylmethylcarbinols.*

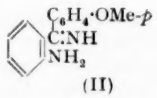
By A. J. Nunn and K. Schofield.

We have described the preparation of (I; R = 2-pyridyl) and related compounds from 2-pyridylmethyl-lithium and 2-amino-4′-methoxybenzophenone (Nunn and Schofield, *J.*, 1952, 589). The preparation by Brown and Murphey (*J. Amer. Chem. Soc.*, 1951, **73**, 3308) of 2-, 3-, and 4-ethylpyridine from methyl chloride and 2-, 3-, and 4-picoline in the presence of sodamide or potassamide in liquid ammonia suggested the use of similar methods for the synthesis of (I; R = 3- and 4-pyridyl). For comparison with the earlier experiments using 2-pyridylmethyl-lithium, 2-amino-4′-methoxybenzophenone was also treated with two equivalents of 2-picoline and sodamide in liquid ammonia. The yield of (I; R = 2-pyridyl) was approximately the same from both reactions (*ca.* 50%). Yields of (I; R = 3-pyridyl) from 3-picoline by the sodium method were lower, but were improved by using a larger excess of the reagent.

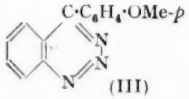
By treatment of 2-amino-4′-methoxybenzophenone with 4-picoline and sodamide in liquid ammonia a yellow compound $C_{14}H_{14}ON_2$ was obtained. This also resulted when the 4-picoline was omitted and was clearly 2-amino-4′-methoxybenzophenone imine (II). It was hydrolysed by hot dilute acid, or by passage in benzene over alumina, to the parent ketone, and on diazotisation provided the yellow 4-*p*-methoxyphenylbenzotriazine (III). The formation of ketimines by this method does not appear to have been observed previously, and the synthesis of a benzotriazine from an unmodified ketimine also appears to be new.



(I)



(II)



(III)

Experimental.—1-o-*Aminophenyl*-1-p-*methoxyphenyl*-2-2′-*pyridylethanol.* To a suspension of sodamide [prepared according to Vaughn, Vogt, and Nieuwland (*J. Amer. Chem. Soc.*, 1934, **56**, 2120) from 2·5 g. of sodium] in liquid ammonia (150 c.c.), 2-picoline (9·3 g., 0·1 mole) was added during 5 minutes and the red solution was stirred for ½ hour. 2-Amino-4′-methoxybenzophenone (11·4 g., 0·05 mole) in 2-picoline (5 c.c.) and dry ether (40 c.c.) was added during 10 minutes, the mixture was stirred for 4 hours, the ammonia allowed to evaporate, and the residue then decomposed with wet ether (100 c.c.) and water (30 c.c.). The yellow solid (10·8 g.; m. p. 128—150°) which separated crystallised from methanol (charcoal) as needles of 1-*o*-aminophenyl-1-*p*-methoxyphenyl-2-2′-pyridylethanol (8·0 g., 49·6%), m. p. 154—155°, identical with an authentic specimen (Schofield, *J.*, 1949, 2408).

1-o-*Aminophenyl*-1-p-*methoxyphenyl*-2-3′-*pyridylethanol.* 2-Amino-4′-methoxybenzophenone (7·6 g., 0·03 mole) in 3-picoline (4 c.c.) and dry ether (30 c.c.) was added to 3-pyridylmethylsodium [0·1 mole, formed by stirring 3-picoline (9·3 g.) for 3 hours with sodamide [from 2·5 g. of sodium) in liquid ammonia (150 c.c.)], the reaction mixture was worked up as described above, and the product was extracted with ether. The red gum remaining after removal of the dried (Na_2SO_4) solvent crystallised from benzene–ligroin (b. p. 60—80°) and the resulting yellow crystals were digested with hot benzene (20 c.c.). The residue remaining on cooling (2·1 g.; m. p. 135—145°) gave crystals (1·6 g., 14·5%; m. p. 161—163°) from aqueous alcohol. The *alcohol* separated from ethanol as needles, m. p. 169—170° (Found: C, 75·4; H, 6·1. $C_{20}H_{20}O_2N_2$ requires C, 75·0; H, 6·3%).

2-*Amino*-4′-*methoxybenzophenone imine.* (*a*) 4-Pyridylmethylsodium (0·1 mole, prepared from 4-picoline as described for the 3-isomer) was treated with 2-amino-4′-methoxybenzophenone (7·6 g.) in 4-picoline (4 c.c.) and ether (30 c.c.). The mixture was stirred for 4 hours, left overnight, and then decomposed with wet ether. The red gum, obtained from the ethereal extract, was dissolved in alcohol (8 c.c.) and the yellow *imine* (5·0 g.; m. p. 75—90°) which separated on cooling was recrystallised from benzene and then from alcohol as prisms (2·8 g., 26·1%), m. p. 91—92° (Found: C, 73·6; H, 6·2; N, 12·7. $C_{14}H_{14}ON_2$ requires C, 74·3; H, 6·2; N, 12·4%).

When the reaction time was doubled, a 29·4% yield resulted.

(*b*) 2-Amino-4′-methoxybenzophenone (7·6 g., 0·03 mole) in dry pyridine (4 c.c.) and ether (25 c.c.) was added during 5 minutes to a suspension of sodamide (from 2·5 g. of sodium) in liquid ammonia (200 c.c.). The mixture was stirred for 3 hours, left overnight, and decomposed with wet ether. The ethereal extract was washed with water and dried (Na_2SO_4). Removal of the solvent left a red gum which on dissolution in hot ethanol (8 c.c.) gave yellow crystals (3·6 g.), m. p. 85—87°. Yellow prisms (2·57 g.), m. p. 87—88°, separated from aqueous ethanol and gave a mixed m. p. of 88—90° with 2-amino-4′-methoxybenzophenone imine (m. p. 91—92°).

4-p-*Methoxyphenylbenzotriazine.* The imine (0·25 g.) in hydrochloric acid (10 c.c.; 2N) was treated at 0° with aqueous sodium nitrite (3 c.c.; 5%), whereupon a yellow solid (0·25 g.), m. p. 138—139°, separated immediately. Recrystallisation from benzene gave yellow plates of 4-p-*methoxyphenylbenzotriazine*, m. p. 138—139° (Found: C, 70·5; H, 4·6; N, 16·9. $C_{14}H_{11}ON_3$ requires C, 70·9; H, 4·7; N, 17·7%).

We are indebted to the Council of University College, Exeter, and to Imperial Chemical Industries Limited for financial support.

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, October 24th*, 1952.]

149. *An Improved Preparation of Phenanthridine.*

By D. W. OCKENDEN and K. SCHOFIELD.

SEVERAL methods of obtaining phenanthridine have been described (Theobald and Schofield, *Chem. Reviews*, 1950, **46**, 171; Badger, Seidler, and Thomson, *J.*, 1951, 3207), but the simplest, the cyclisation of 2-formamidodiphenyl, has hitherto yielded only 42% of the base [zinc chloride being the cyclising agent (Morgan and Walls, *J.*, 1932, 2225)], and involves a somewhat tedious purification. Recent demonstrations of the value of the combined action of stannic chloride and phosphorus oxychloride in cyclisations of this type (Barber *et al.*, *J. Soc. Chem. Ind.*, 1950, **69**, 82; Petrow and Wragg, *J.*, 1950, 3516; Nunn, Schofield, and Theobald, *J.*, 1952, 2797) suggested their application to 2-formamidodiphenyl. Several experiments indicated the advantage of using 2 mols. of stannic chloride, the yield of phenanthridine thus being raised to 90%.

Phenanthridine.—2-Formamidodiphenyl (Pictet and Hubert, *Ber.*, 1896, **29**, 1182) (10 g.), phosphorus oxychloride (50 c.c.), nitrobenzene (100 c.c.), and anhydrous stannic chloride (5·4 g.) were refluxed for 4 hours. The solvent was removed by steam-distillation, and the residual suspension was basified with ammonia solution. The product was crystallised from ligroin (b. p. 60—80°) giving phenanthridine (7·7 g.; 90%), m. p. 105—106° (Found: C, 87·0; H, 5·1. Calc. for $C_{13}H_9N$: C, 87·1; H, 5·1%).

The authors are grateful to the Council of University College, Exeter, and to Imperial Chemical Industries Limited for financial support, and to D.S.I.R. for a maintenance grant to one of them.

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, October 24th*, 1952.]

OBITUARY NOTICE.

J. C. E. SIMPSON.

1908—1952.

JAMES CHARLES EDWARD SIMPSON was born in Wallasey, Cheshire, on August 14th, 1908, and died on February 7th, 1952, after a series of operations at Wrexham Hospital.

He was educated at St. Edward's School, Oxford, and at the University of Liverpool where he graduated in 1929, was awarded the Leverhulme Chemistry Prize and the Campbell Brown Fellowship, and began work under Professor (now Sir Ian) Heilbron on researches in the sterol group. These were chiefly concerned with the elucidation of the chemistry of ergosterol, and from studies on the oxidation of α- and β-ergostenol and their derivatives (Heilbron, Simpson, and Wilkinson, *J.*, 1932, 1699; Simpson and Morrison, *J.*, 1932, 1710; Heilbron, Morrison, and Simpson, *J.*, 1933, 302) additional convincing evidence was obtained concerning the nuclear identity of ergosterol and the bile acids (cf. also Heilbron, Simpson, and Samant, *J.*, 1933, 1410). Analysis of bromine-substitution products confirmed the C_{28} formula for ergosterol (Heilbron and Simpson, *J.*, 1932, 2400), and the isolation from the oxidation of ergostanol of a methyl ketone, $C_9H_{18}O$, distinct from the *iso*hexyl methyl ketone obtained from cholesterol under similar conditions, indicated that the additional carbon atom was present in the side chain (*loc. cit.*, p. 1699).

The importance of the researches on ergosterol in which Simpson played a prominent part is made clear in the account given before the Chemical Society in December 1932 (Heilbron, Simpson, and Spring, *J.*, 1933, 626).

In 1933 he was awarded a Commonwealth Fund Fellowship and spent the next two years with Dr. W. A. Jacobs at the Rockefeller Institute for Medical Research, New York. Simpson's earlier experience with sterols stood him in good stead in his collaboration on problems connected with the digitalis sapogenins. The first definite information that this group of sapogenins contains the typical steroid skeleton came with the isolation by Jacobs and Simpson (*J. Biol. Chem.*, 1934, **105**, 501) of Diels' hydrocarbon on selenium dehydrogenation of sarsasapogenin; the same hydrocarbon was obtained by similar treatment of gitogenin (*J. Amer. Chem. Soc.*, 1934, **56**, 1424). Other observations indicated a C_8 side chain in the sapogenins and this correlation of the general structure of sarsasapogenin and gitogenin was extended to that of tigogenin (Jacobs and Simpson, *J. Biol. Chem.*, 1935, **110**, 429).

Simpson became an Assistant Lecturer at King's College, London, on his return from America and began independent work on natural products, beginning with an investigation of Senega root (*J.*, 1937, 730) and the ether-soluble components from sarsaparilla root (Simpson and Williams, *J.*, 1937, 733; 1938, 2040).

Simpson's work between 1938 and 1944 was largely concerned with triterpenes. He showed (Simpson and Williams, *J.*, 1938, 686, 1712) that β-boswellic acid was a β-hydroxy-acid, and that its double bond was in a similar environment to that in α- and β-amyrin. Much effort was devoted to attempts to determine the detailed structure of rings C—E of the β-amyrin group of triterpenes (*loc. cit.*; *J.*, 1943, 477). Continuing his examination of natural products, and making use of chromatography on alumina—then a very novel procedure—he isolated three new alcohols from dandelion root: taraxol, taraxerol, and ψ-taraxasterol (Burrows and Simpson, *J.*, 1938, 2042). The last, together with a precursor, ψ-taraxastanediol, was also isolated from the minor constituents of Manila elemi resin. In this case a further alcohol, maniladiol, was obtained for the first time, whilst the technique for isolating brein was considerably improved (Morice and Simpson, *J.*, 1940, 795; *J.*, 1941, 181). Finally (*J.*, 1944, 283), *Lactucarium germanicum* yielded a new alcohol, germanicol, which was to become of considerable importance in the final elucidation of the stereochemistry of the β-amyrin group of triterpenes.

In 1939 Simpson was appointed to a temporary lectureship in Durham Colleges in the University of Durham. Soon after his arrival he became interested in the chemistry of cinnoline, a heterocyclic system which had been almost completely neglected since the discovery of the first derivative in 1883. Simpson's contribution to cinnoline chemistry was the generalisation of the existing fortuitous syntheses, the determination of the factors affecting the extent of cinnoline formation and hence a mechanism for the process, and, finally, a study of the properties of cinnolines.

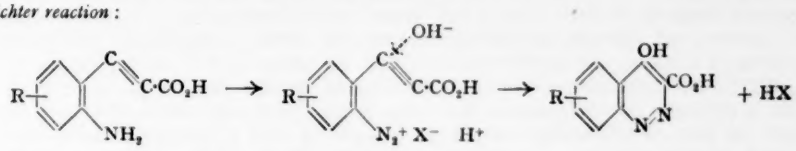
At this time cinnoline derivatives had been obtained by Richter (1883), Widman (1884), Stoermer (1909), and Borsche (1941).

New examples of the Widman–Stoermer reaction (see below) were presented in " Cinnolines. Part I " (Simpson and Stephenson, *J.*, 1942, 353), and the effect of substituents R′ and R″

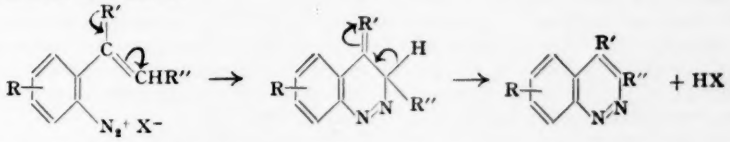
(see below) on the cyclisation of diazotised *o*-aminoarylethylenes was studied (*J.*, **1943**, **447**); the steric factors involved were also considered (*J.*, **1946**, **673**). Extension of the reaction to simple 4-methylcinnolines came later (Atkinson and Simpson, *J.*, **1947**, **808**).

Generalisation of the Richter reaction by Schofield and Simpson (Part III, *J.*, **1945**, **512**) was accompanied by suggested possible mechanisms for this reaction. This study was continued in Part IV (Schofield and Simpson, *J.*, **1945**, **520**) with extensions to the Borsche reaction, a number of *Bz*-substituted 4-hydroxycinnolines being prepared from the corresponding *o*-aminoacetophenones. Further, a most important conclusion was reached that the three main reactions were to be considered " essentially manifestations of the same fundamental process."

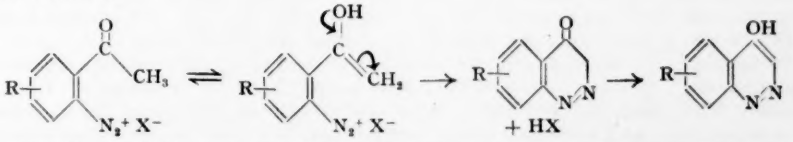
Richter reaction :



Widman–Stoermer reaction :



Borsche reaction :



The Borsche synthesis was considered the best route to 4-hydroxycinnolines and was exploited with much success by Simpson and his co-workers in the preparation of the following derivatives : **6** : **7**- and **7** : **8**-disubstituted (*J.*, **1947**, **227**), 7-chloro- (*J.*, **1947**, **232**), 3-methyl- (*J.*, **1948**, **354**), 8-nitro-, *Bz*-methyl- (*J.*, **1948**, **1702**), and 3-ethyl-4-hydroxy-cinnoline, and β-(4-hydroxy-3-cinnolyl)propionic acid (*J.*, **1948**, **2318**). A modified mechanism for the Borsche synthesis, involving acid-catalysed enolisation of the ketonic side chain, was advanced by Schofield and Simpson (*J.*, **1948**, **1170**) to account for the beneficial effect of high acid concentration on cinnoline formation in those cases where the *Bz*-substitution tends to reduce the electrophilic activity of the diazonium ion. In all this work much effort was expended in preparing intermediates of established structure. The importance of good routes to *o*-aminoketones for other syntheses besides those of cinnolines led to Simpson's earlier publication of a critical survey of such routes (*J.*, **1945**, **646**).

Probably the most interesting reaction encountered in the cinnoline field, and apparently specific to it, is that discovered by Schofield and Simpson (*J.*, **1946**, **472**) when trying to acetylate 4-hydroxycinnoline-3-carboxylic acid with pyridine–acetic anhydride.

Methylation of several 4-hydroxycinnolines was studied and the nitration of 4-hydroxycinnoline itself was investigated (*J.*, **1946**, **480**; *J.*, **1947**, **237**). Reference has been made to 4-methylcinnolines (*J.*, **1947**, **808**), the methyl group of which was shown to be reactive and hence N^1 is the basic centre of the molecule; further studies (Simpson, *J.*, **1947**, **1653**) designed to confirm this point by alkaline degradation of cinnolinium salts showed the importance of the nature of the 4-substituent on such decompositions. The extent to which cinnolines may be regarded as cyclic azo-compounds was superficially examined (Atkinson and Simpson, *J.*, **1947**, **1649**) through the properties of some *N*-oxides and the reduction of cinnolines to indoles.

Some of the reactions studied by Simpson and his co-workers not only disclosed fundamental properties of the cinnoline ring system, but were valuable sources of materials for other researches. A particular example of this type of work was Simpson's war-time collaboration with Imperial Chemical Industries Limited on the preparation of potential antimalarials (Schofield and Simpson, *Nature*, **1946**, **157**, **439**; Keneford and Simpson, *J.*, **1947**, **917**; Keneford, Schofield, and Simpson, *J.*, **1948**, **358**).

In discussing his attraction by heterocyclic chemistry Simpson often referred to his intense

distaste for the subject as a student owing to " the presentation of an apparently endless series of syntheses of compounds having illogical names and systems of numbering, little mention being made of their properties." Consequently his work on cinnoline was always discussed with reference to comparable results in other heterocyclic types. This characteristic enthusiasm for correlating data from related topics found expression in a new series of papers including work on quinolines and quinazolines.

The first paper (Morley and Simpson, *J.*, **1948**, 360) described reactions of 6- and 7-nitro-4-hydroxyquinazoline. The possibility of reaction between 4-chloroquinazolines and amines (Part II, Morley and Simpson, *J.*, **1949**, 1014) was related to the pK_a values of the amines and, in heterocylic amines, to the possibility of prototropy to the dihydroimino-form. In Part III (Morley and Simpson, *J.*, **1949**, 1354) it was shown that the basic centre of 4-phenoxyquinazoline is N^1. Aspects of quinoline chemistry investigated (with Wright) were the synthesis of derivatives of 4-chloro- and 6-nitro-quinoline and the nitration of 4-aminoquinoline (*J.*, **1948**, 1707, 2023); 3-nitroquinolines were also synthesised (Morley and Simpson, *J.*, **1948**, 2024). Simpson's emphasis on comparative chemistry became dominant about this time, the basic strength of some 4-substituted cinnolines, quinolines, and quinazolines being determined (Keneford, Morley, Simpson, and Wright, *J.*, **1949**, 1356). The qualitative expressions of chemical reactivity which had been amassed by Simpson and his co-workers were summarised (*J.*, **1950**, 1104) and discussed with reference to the predictions arising from the calculation of electron densities by Longuet-Higgins and Coulson in the parent systems. Simpson's earlier collaboration with Professor R. A. Morton was renewed in connection with this work, and ultra-violet absorption spectra of compounds in the three series, quinolines, quinazolines, and cinnolines, were interpreted (with Miss J. M. Hearn, *J.*, **1951**, 3318).

Most of the antimalarial work was carried out at the Warrington Yorke Department of Chemotherapy in the Liverpool School of Tropical Medicine where Simpson held an I.C.I. Fellowship from **1945**, the year in which he was awarded the D.Sc. of Liverpool University. In **1946** he was appointed to the staff of the Medical Research Council and began work in collaboration with Dr. E. M. Lourie (then Director of the Department) on the chemotherapy of trypanosomiasis; this was continued after **1949** in the Chemistry Department of Manchester University where Simpson was Director of the Council's Group for Research in Chemotherapy. The comparative work outlined above formed part of this project. The discovery of trypanocidal activity in crude preparations of 4 : 6-diaminocinnolinium salts and its absence in the pure compounds led to the hypothesis (Keneford, Lourie, Morley, Simpson, Williamson, and Wright, *J.*, **1952**, 2595) that it was due to products of incomplete reduction such as the biscinnolinium azo-compounds. A few of these compounds (McIntyre and Simpson, *J.*, **1952**, 2606, 2615) and the quinoline analogues (Macey and Simpson, *J.*, **1952**, 2602) were prepared and the original assumption fully supported by the high activity of one form of the cinnolinium compounds. An extension of the hypothesis to include biscinnolinium salts with bridge groups other than $^-N{=}N^-$ (Morley and Simpson, *J.*, **1952**, 2617) led to N^1N^3-di-(4-amino-6-cinnolyl)guanidine dimethiodide, a compound of the same order of activity as " Antrycide " (Morley, Lourie, Simpson, and Walker, *Brit. J. Pharmacol.*, **1951**, **6**, 643). Other work in this field (with Atkinson, Brown, and Taylor, unpublished) was being actively pursued at the time of Simpson's death, but he regarded the synthesis of a highly active compound as something incidental in a programme designed to discover a fundamental relation between biological activity and chemical constitution.

Simpson's expert knowledge of cinnolines and his keen interest in related heterocylic types are evident in his volume on " Condensed Pyridazine and Pyrazine Rings " in the Interscience Series on Heterocyclic Compounds.

To his leisure hours he brought the same energetic qualities which characterised his research and teaching. He enjoyed a fast game of tennis or badminton and spent many of his holidays fell-walking in the Lake District. An early interest in bell-ringing at St. Mary's Church, Liscard, where his father, later Residentiary Canon of Chester Cathedral, was the Vicar, developed throughout his life. In this connection his expression as a conductor and his stamina and artistry in the handling of bells is fully described in " *The Ringing World* " (**1952**, **48**, 105); he was also well-known in choral societies.

The extent and quality of Simpson's publications are not only proof of his intense intellectual and physical energy but reveal the degree to which he was able to inspire in his research students, always small in number, the same enthusiasm for the problems in hand; that he was able, simultaneously, to gain their confidence as a friend is a measure of his personal qualities. Our loss of an able colleague and understanding teacher is indeed great and our sympathy is with his mother and brother who survive him.

C. M. Atkinson.

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